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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
C07D 239/54, A61K 31/505 C07D 239/56	A1	WO 94/01414
		(43) International Publication Date: 20 January 1994 (20.01.94)

(21) International Application Number: PCT/GB93/01443

(22) International Filing Date: 9 July 1993 (09.07.93)

(30) Priority data:
9214720.6 10 July 1992 (10.07.92) GB

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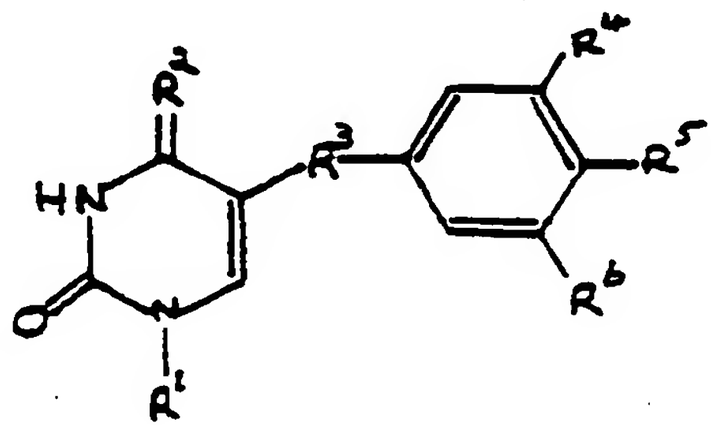
(81) Designated States: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: URACIL DERIVATIVES AS ENZYME INHIBITORS



(I)

(57) Abstract

Novel uracil derivatives of formula (I) and esters and prodrugs thereof wherein R^1 is H, C_{1-8} straight or branched-chain alkyl, C_{2-6} alkenyl, or (C_{1-3} alkyl-C_{3-6} cycloalkyl-C_{1-3} alkyl) optionally substituted by 1 or 2 substituents selected from $-OR^8$ or $-NR^8R^9$ (wherein R^8 and R^9 are the same or different and are selected from H, C_{1-6} straight or branched-chain alkyl, and aralkyl); or a $-CH_2ZR^{10}$, $-ZCH_2R^{10}$, or $CH_2ZR^{10a}ZR^{10}$ group (wherein R^{10a} is selected from C_{1-6} straight or branched-chain alkylene and R^{10} is selected from C_{1-6} straight or branched chain alkyl) each of R^{10a} and R^{10} being optionally substituted by 1 or 2 substituents independently selected from $-OR^8$ and $-NR^8R^9$ (wherein R^8 and R^9 are as defined above) and Z is selected from O, S, $-CH_2O-$, or $-CH_2S-$); R^2 is selected from O or S; R^3 is selected from O, S, -SO, $-SO_2$, $-NR^8$, C=O, or $-C_{1-6}$ straight or branched-chain alkyl; R^4 is selected from H, C_{1-4} straight or branched-chain alkyl, halogen, $-OR^{11}$ (wherein R^{11} is C_{1-4} straight or branched-chain alkyl optionally substituted by halogen, aryl, C_{3-6} cycloalkyl, (C_{1-3} alkyl-C_{3-6} cycloalkyl), C_{2-6}alkenyl or C_{2-6}alkynyl), methylenedioxy, $-CX_3$ (wherein X is halogen), NO_2, or CN; R^5 is selected from H, halogen or $-OR^{11}$; R^6 is selected from H, or Y-Ar-$R^7_{(m)}$ (wherein Y is selected from O, S, -SO, $-SO_2$, $-NR^8$, C=O, or $-C_{1-6}$ straight or branched-chain alkyl, Ar is phenyl or naphthyl, m is 1-3 and R^7 is selected from R^8, $-CO_2R^8$, $-COR^8$, $-CONR^8R^9$, $R^{8a}OR^8$ (wherein R^{8a} is selected from C_{1-6} straight or branched-chain alkyl, and aralkyl), -CN, $-CX_3$ (wherein X is halogen), $-OR^8$, OCX_3 (wherein X is halogen), $-SR^8$, $-SO_2R^8$, $-OR^{8a}O-$ (when m=1), $-NO_2$, $-NR^8R^9$, $-NHCOR^8$, $-NHSO_2R^8$, fluoro, chloro, bromo, or iodo, or a combination thereof); provided that when R^1 is H, $CH_2OCH_2CH_2OH$ or $CH_2OCH(CH_2OH)_2$, R^2 is O, R^3 is $-CH_2$ then R^4, R^5 and R^6 are other than $-OCH_3$, $-OCH_2CH_3$, $-OCH_2Ph$, or -O-iso-propyl, pharmaceutical compositions containing them, their uses in medicine and the preparation of such compounds are disclosed.

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URACIL DERIVATIVES AS ENZYME INHIBITORS

The present invention relates to certain enzyme inhibitors which are especially useful for co-administration with other therapeutic compounds such as antiviral compounds in order to provide an improved therapeutic effect including reduction in toxic side-effects.

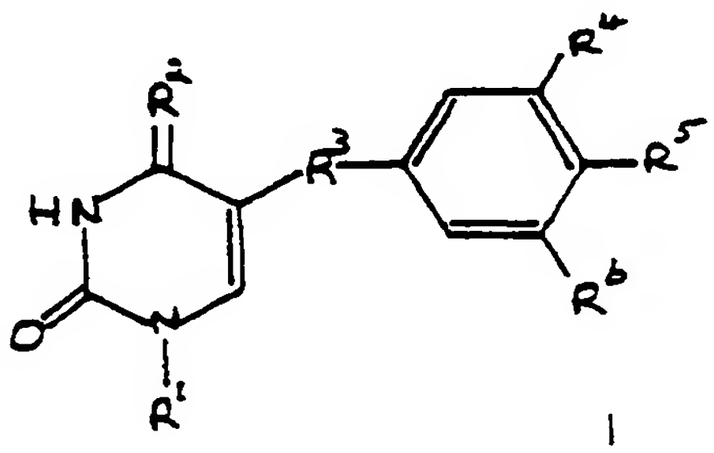
A therapeutic nucleoside that has been found to have a particularly beneficial clinical effect against a spectrum of conditions associated with Human Immunodeficiency Virus (HIV) infections such as Acquired Immune Deficiency Syndrome (AIDS), AIDS-related complex (ARC) and asymptomatic infections, is the compound 3'-azido-3'-deoxythymidine(AZT) having the approved name zidovudine. This compound at low doses is generally very well tolerated by patients and is now widely used in the treatment of HIV infections. However, in certain patients treated with zidovudine, some haematological suppression including anaemia and neutropenia may be observed, presumably arising from a certain limited level of toxicity of zidovudine observed towards stem cells. Other less commonly observed side-effects have been described such as myopathy which may be related to intracellular activity of zidovudine.

Recently, it has been found that uridine and cytidine could reverse the toxic effect of zidovudine in vitro(Sommadosi, et al., Antimicrobial Agents Chemo., 1987, 31:453-454). However, uridine is toxic to humans when given via continuous infusion in vivo. When uridine is administered to a patient in an intermittent schedule, it is rapidly eliminated from the plasma(van Groeniger, et al., 1986, Cancer Treatment Rept. 70:745-750).

US patent 4,874,602 describes the use of 5-benzylacyclouridine(BAU) for the reduction of the severity of anemia induced by the administration of zidovudine. This compound has been described as an inhibitor of the enzyme uridine phosphorylase which is responsible for the cleavage of uridine to uracil(Niedzwicki, et al., Biochem. Pharmacol., 1982, 31:1857-1861). Several derivatives of BAU have been shown to be superior to BAU in their ability to inhibit uridine phosphorylase(Naguib, et. al., Biochem. Pharmacol. 1987, 36:2195-2201). Certain 5-benzyl barbituate compounds have been described as uridine phosphorylase inhibitors which are useful for reducing

the toxicity and anemia induced by antiviral drugs, such as AZT, as well as for potentiating anticancer drugs and combatting their host-toxicity(PCT Publication No. WO 91/16315). Furthermore, benzyloxy derivatives of BAU have been reported to decrease the bone marrow toxicity of pyrimidine nucleoside analogs, such as AZT(published under WO 89/09603, October 19, 1989, PCT/US89/01528). Recently issued US Patent 5,077,280 discloses a treatment for AIDS-type diseases in which a pyrimidine nucleoside compound, such as AZT, and a uridine phosphorylase inhibitor are co-administered either simultaneously or sequentially to treat the viral infection and protect or rescue uninfected cells in the afflicted subject.

It has now been found that a class of uracil derivatives are potent inhibitors of the uridine phosphorylase enzyme. Accordingly the present invention provides a compound of formula (I)



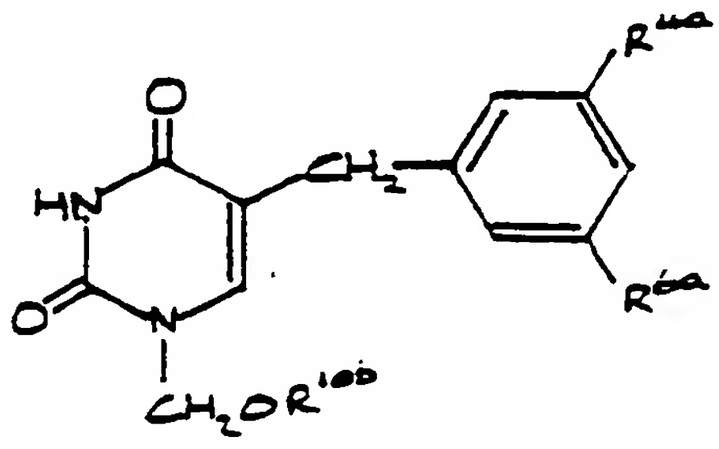
I

wherein R^1 is H, C_{1-8} straight or branched-chain alkyl, C_{2-6} alkenyl, or (C_{1-3} alkyl-C_{3-6} cycloalkyl-C_{1-3} alkyl) optionally substituted by 1 or 2 substituents selected from $-OR^8$ or $-NR^8R^9$(wherein R^8 and R^9 are the same or different and are selected from H, C_{1-6} straight or branched-chain alkyl, and aralkyl); or a $-CH_2ZR^{10}$, $-ZCH_2R^{10}$, or $CH_2ZR^{10a}ZR^{10}$ group(wherein R^{10a} is selected from C_{1-6} straight or branched-chain alkylene and R^{10} is selected from C_{1-6} straight or branched chain alkyl) each of R^{10a} and R^{10} being optionally substituted by 1 or 2 substituents independently selected from $-OR^8$ and $-NR^8R^9$(wherein R^8 and R^9 are as defined above) and Z is selected from O, S, $-CH_2O-$, or $-CH_2S-$); R^2 is selected from O or S; R^3 is selected from O, S, -SO, $-SO_2$, $-NR^8$, C=O, or $-C_{1-6}$ straight or branched-chain alkyl(e.g., $-CH_2-$); R^4 is selected from H, C_{1-4} straight or branched-chain alkyl, halogen, -

OR^{11}(wherein R^{11} is C_{1-4} straight or branched-chain alkyl optionally substituted by halogen, aryl, C_{3-6} cycloalkyl, (C_{1-3} alkyl-C_{3-6} cycloalkyl), C_{2-6} alkenyl or C_{2-6} alkynyl), methylenedioxy, $-CX_3$(wherein X is halogen, preferably fluoro), NO_2, or CN; R^5 is selected from H, halogen or $-OR^{11}$; R^6 is selected from H, or Y-Ar-$R^7{}_{(m)}$(wherein Y is selected from O, S, -SO, $-SO_2$, $-NR^8$, C=O, or $-C_{1-6}$ straight or branched-chain alkyl(e.g., $-CH_2$), Ar is phenyl or naphthyl, m is 1-3 and R^7 is selected from R^8, $-CO_2R^8$, $-COR^8$, $-CONR^8R^9$, $R^{8a}OR^8$(wherein R^{8a} is selected from C_{1-6} straight or branched-chain alkyl, and aralkyl), -CN, $-CX_3$(wherein X is halogen, e.g., fluoro), $-OR^8$, OCX_3(wherein X is halogen, e.g., fluoro), $-SR^8$, $-SO_2R^8$, $-OR^{8a}O-$(when m=1), $-NO_2$, $-NR^8R^9$, $-NHCOR^8$, $-NHSO_2R^8$, fluoro, chloro, bromo or iodo, or a combination thereof); and esters and prodrugs thereof (including amino acid esters, e.g., valyl or iso-leucyl) of the alcohols; provided that when R^1 is H, $CH_2OCH_2CH_2OH$ or $CH_2OCH(CH_2OH)_2$, R^2 is O, R^3 is $-CH_2$, then R^4, R^5 and R^6 are other than $-OCH_3$, $-OCH_2CH_3$, $-OCH_2Ph$, or -O-iso-propyl.

Preferred compounds of formula (I) are those of formula (IA) and esters and prodrugs thereof

(IA)



wherein R^{10b} is a C_{2-3} straight or branched chain alkyl group substituted by one or two hydroxyl groups; R^{4a} is H or $-OR^{11a}$ wherein R^{11a} is a C_{3-5} straight or branched chain alkyl group optionally substituted by fluoro; and R^{6a} is H or -O-Ar-R^{7a} wherein Ar is phenyl and R^{7a} is fluoro, chloro or cyano; provided that one but not both of R^{4a} and R^{6a} is H.

The compounds of formula (IA) and esters and prodrugs thereof, wherein R^{10b} is CH_2CH_2OH, $CH(CH_2OH)_2$, and R^{4a} is $-OCH_2CH_2CH_3$, or $-OCH(CH_3)CH_2CH_3$ and R^{6a} is H are more preferred compounds of the invention.

The compounds of formula (IA) and esters and prodrugs thereof, wherein wherein R^{10b} is CH_2CH_2OH, $CH(CH_2OH)_2$, R^{4a} is H and R^{6a} is -O-Ar-R^{7a} wherein Ar is

phenyl and R^{7a} is H, fluoro, chloro or cyano are a further preferred group of compounds of the invention.

The compounds of formula (IA) and esters and prodrugs thereof, wherein R^{10b} is CH_2CH_2OH or $-CH(CH_2OH)_2$, R^{4a} is H, and R^{6a} is is $-O-Ar-R^{7a}$ wherein Ar is phenyl and R^{7a} is 3-fluoro, 3-chloro or 3-cyano are most preferred compounds of the invention.

It will be appreciated by the skilled practicioner that the amino acid esters of the compounds of the present invention can be in the D, L, or DL configuration with the L configuration preferred.

According to the present invention, the compounds of formula (I) or (IA), or prodrugs thereof, may be in the form of their pharmaceutically acceptable addition salts, which are preferably non-toxic base salts and include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium, salts with organic bases such as dicyclohexylamine and N-methyl-D-glutamine, and salts with amino acids such as arginine and lysine.

Preferably the compounds of the present invention are in the non-salt form.

Prodrugs of the uracil derivatives defined hereinbefore are compounds which may be metabolised in vivo to give the corresponding uracil derivatives. These prodrugs may or may not have activity in their own right but will normally have some activity. Such prodrugs may possess substituents on the unsubstituted N-3 of the compounds of formula I such as $-COR^8$, $-CSR^8$, $-CONR^8R^8$, $-COOR^8$, $-CH_3$, $-CH(CH_3)_2$, $-CR^8R^8OCR^8R^8OCOR^8$(wherein R^8 is as defined hereinbefore), $-CO_2CH_2Ph$, or $-CH_2R^{8b}$(wherein R^{8b} is $-OCOR^8$, $-OCSR^8$, $-OR^8$, $-OCO(CH_2)_nNR^8R^8$, $-OPO_3^=$, OSO_3^-, $-OC(O)(CH_2)_nCO_2R^8$, $-OCR^8R^8OH$, $-NR^8R^8$, NR^8COR^8(wherein R^8 is as defined hereinbefore and n=1-4). In addition, compounds of formula I in which the -OH functionality of R^1 is replaced by $-OR^{9a}$(wherein R^{9a} is selected from C_{1-6} straight or branched-chain alkyl, and aralkyl)may also act as prodrugs, $-COR^8$, $-CSR^8$, $-COCR^8R^8NR^8R^8$, $-CSCR^8R^8NR^8R^8$, $-CR^8R^8OCOR^8$, $-SO_2OR^8$, $-PO(OR^8)_2$ or $-PS(OR^8)_2$(wherein R^8 is as defined hereinbefore).

Particularly preferred compounds of formula I in accordance with the invention are:
1-((2-hydroxyethoxy)methyl)-5-(3-propoxybenzyl)uracil,
1-((2-hydroxyethoxy)methyl)-5-(3-sec-butoxybenzyl)uracil,
1-((2-hydroxyethoxy)methyl)-5-(3-phenoxybenzyl)uracil,
1-((2-hydroxyethoxy)methyl-5-(3-(3-fluorophenoxy)benzyl)uracil,
1-((2-hydroxyethoxy)methyl)-5-(3-(3-chlorophenoxy)benzyl)uracil and
1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(3-cyanophenoxy)benzyl)uracil.

The most preferred compounds of formula I in accordance with the invention are:
1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-phenoxybenzyl)uracil,
1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(3-fluorophenoxy)benzyl)uracil,
1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(4-fluorophenoxy)benzyl)uracil,
1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(3-chlorophenoxy)benzyl)uracil and
1-((2-hydroxyethoxy)methyl)-5-(3-(3-cyanophenoxy)benzyl)uracil.

Other preferred compounds include:
1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-propoxybenzyl)uracil,
1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-chlorobenzyl)uracil,
2-((5-(3-chlorobenzyl)-1,2,3,4-tetrahydro-2,4-dioxo-1-pyrimidinyl)methoxy)ethyl acetate,
5-(3-chlorobenzyl)-1-((2-hydroxyethoxy)methyl)uracil,
5-(3-chlorobenzyl)-1-(4-hydroxybutyl)uracil,
1-((2-hydroxyethoxy)methyl)-5-(3-allyloxybenzyl)uracil,
1-((2-hydroxyethoxy)methyl)-5-(3-(3-fluoropropoxy)benzyl)uracil,
1-((2-hydroxyethoxy)methyl)-5-(3-sec-butoxybenzyl)uracil,
1-((2-hydroxyethoxy)methyl)-5-(3,5-difluorobenzyl)uracil,
1-((2-hydroxyethoxy)methyl)-5-(3-trifluoromethoxybenzyl)uracil,
1-((2-hydroxyethoxy)methyl)-5-(3-(4-fluorophenoxy)benzyl)uracil,
3-(3-(2-fluorophenoxy)phenyl)propionate,
1-((2-hydroxyethoxy)methyl)-5-(3-(4-chlorophenoxy)benzyl) uracil,
1-((2-hydroxyethoxy)methyl)-5-(3-(4-methoxyphenoxy)benzyl) uracil,
1-((2-Hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(3-trifluoromethylphenoxy)benzyl)uracil,
1-((2-hydroxyethoxy)methyl)-5-(3-(3-methoxyphenoxy)benzyl) uracil,

1-((2-Hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(3-methoxyphenoxy)benzyl)uracil,
1-((2-hydroxyethoxy)methyl)-5-(3-(4-cyanophenoxy)benzyl)uracil,
1-((2-Hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(4-cyanophenoxy)benzyl)uracil,
1-((2-hydroxyethoxy)methyl)-5-(3-(4-trifluoromethylphenoxy)benzyl)uracil,
1-((2-Hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(4-trifluoromethylphenoxy)benzyl)uracil,
1-((2-hydroxyethoxy)methyl)-5-(3-(4-methylphenoxy)benzyl)uracil,
1-((2-Hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(4-methylphenoxy)benzyl)uracil,
1-((2-hydroxyethoxy)methyl)-5-(3-(3-methylphenoxy)benzyl)uracil,
1-((2-Hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(3-methylphenoxy)benzyl)uracil,
1-((2-hydroxy-1-(aminomethyl)ethoxy)methyl)-5-(3-phenoxybenzyl)uracil,
1-((2-aminoethoxy)methyl)-5-(3-phenoxybenzyl)uracil,
1-((2-hydroxy-1-(aminomethyl)ethoxy)methyl)-5-(3-(3-fluorophenoxy)benzyl)uracil,
1-((2-aminoethoxy)methyl)-5-(3-(3-fluorophenoxy)benzyl)uracil,
1-((2-hydroxy(ethylthio))methyl)-5-(3-phenoxybenzyl)uracil,
1-((2-hydroxy(ethylthio))ethoxy)methyl)-5-(3-(3-fluorophenoxy)benzyl)uracil,
1-((2-hydroxyethoxy)methyl)-5-(3-isobutoxybenzyl)uracil and
1-((2-hydroxyethoxy)methyl)-5-(3-butoxybenzyl)uracil.

The compounds of the present invention are useful for the inhibition of the enzyme uridine phosphorylase in mammals(e.g., humans) in need of such enzyme inhibition which comprises administering to a mammal in need thereof an effective amount of a compound of the invention or a pharmaceutical composition comprising a said compound in combination with one or more pharmaceutically acceptable carriers.

The present invention is thus based on the use of compounds of formula I in combination with pyrimidine nucleosides such as zidovudine and reducing the cellular toxicity of the pyrimidine nucleoside, such as the stem cell and haematological toxicity.

According to the present invention therefore we provide a uridine phosphorylase inhibitor, of formula (I) or a prodrug thereof, for use in medicine especially in

combination with pyrimidine nucleosides such as zidovudine for the reduction of pyrimidine nucleoside(e.g.,zidovudine) induced toxicity in mammals(e.g., humans).

In another aspect of the present invention, there is provided a treatment for AIDS-type diseases in which a pyrimidine nucleoside analogue, such as zidovudine, and a uridine phosphorylase inhibitor of the invention are co-administered either simultaneously or sequentially to protect or rescue uninfected cells from the toxic effects of the pyrimidine nucleoside in a mammal(e.g., a human) requiring such treatment.

AIDS-type diseases are defined herein as Acquired Immune Deficiency Disease(AIDS), AIDS-related complex(ARC), asymptomatic HIV infections, as well as any disease which causes a deficiency in the immune system.

Pyrimidine nucleoside analogues which are useful according to the present invention include, for example, 3'-azido-3'-deoxythymidine(AZT); 3'-azido-2',3'-dideoxyuridine(AZddU);
2',3'-dideoxycytidin-2'-ene; 3'-deoxy-3'deoxythymidin-2-ene; and other related compounds.

The compounds of the present invention are not restricted to use for the reduction of zidovudine toxicity. Accordingly, the compounds of the present invention can be utilized to inhibit the enzyme uridine phosphorylase in a mammal(e.g., a human) when such enzyme inhibition is desired. Therefore, other uses of the compounds of the invention which rely on the inhibition of uridine phosphorylase are also encompassed by the present invention. Such uses include: enhancing the antitumor activity of halogenated pyrimidines(e.g., 5-fluoro-2'-deoxyuridine, 5-fluorouridine and 5-fluorouracil) and antineoplastic pyrimidine nucleosides(e.g., 5-fluoro-2'-deoxyuridine(FdUrd), 5-trifluoromethyldeoxyuridine(TFT), and 5-bromovinyldeoxyuridine(BVdU)) which are subject to degradation by uridine phosphorylase. The uridine phosphorylase inhibitors of the present invention are useful for reducing the toxicity of antineoplastic pyrimidine nucleosides as well as for potentiating the efficacy of antineoplastic drugs.

The compounds of the invention can be administered to a mammal either prior to, during or subsequent to administration of the antineoplastic agent. The compounds

are preferably administered prior to administration of the antineoplastic agent to inhibit the uridine phosphorylase enzyme and thereby prevent the degradation of the antineoplastic agent.
The compounds of the present invention can also be used in the treatment of nervous disorders(e.g., schizophrenia and Parkinson's disease) and in the treatment of diseases in which increased levels of uridine are beneficial.

In a further aspect, the present invention provides a uracil derivative as hereinbefore defined for use in the manufacture of a medicament for use in reducing zidovudine induced toxicity or potentiating the antitumor effects of antineoplastic pyrimidine nucleosides, or in the treatment of nervous disorders and diseases in which increased levels of uridine are beneficial.

The present invention further provides :

a) a combination of a uridine phosphorylase inhibitor, as shown in figure I, and zidovudine or a pharmaceutically acceptable salt or ester thereof;

b) a combination of a uridine phosphorylase inhibitor, as shown in figure I, and 5-fluorouracil;

c) a method for the treatment or prophylaxis of an HIV infection in a mammal, including a human, which comprises administering to the said mammal an effective anti-HIV amount of zidovudine or a pharmaceutically acceptable salt or ester thereof in combination with an effective uridine phosphorylase inhibiting amount of a compound of figure I as defined hereinbefore.

d) a method for the treatment or prophylaxis of tumors in a mammal, including a human, which comprises administering to the said mammal an effective anti-tumor amount of 5-fluorouracil in combination with an effective uridine phosphorylase inhibiting amount of a compound of figure I as defined hereinbefore.

Zidovudine(or a pharmaceutically acceptable salt or ester thereof) or an antineoplastic pyrimidine nucleoside, and the said uridine phosphorylase inhibitor may be employed in combination in accordance with the invention by administration of the components of the combination to an appropriate subject either concomitantly, for example in a unitary pharmaceutical formulation, or, more preferably, separately, or sequentially within a sufficient time period whereby the desired therapeutic effect of the combination is achieved.

Zidovudine may be administered per se or in the form of a pharmaceutically acceptable salt, e.g., an alkali metal salt such as sodium or potassium, an alkaline earth salt or ammonium salt. The mono-, di- or triphosphates of zidovudine or their pharmaceutically acceptable base salts(i.e., alkali metal, alkaline earth or ammonium salt) can also be substituted for zidovudine in the combination described by this invention.

Zidovudine or a pharmaceutically acceptable salt or ester thereof and the uridine phosphorylase inhibitor of formula I may be administered respectively for therapy by any suitable route including oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous and intradermal). It will be appreciated that the preferred route will vary with the condition and age of the recipient, the nature of the infection and other clinical factors.

A suitable dose of zidovudine or a pharmaceutically acceptable salt or ester thereof is in the range of 5 to 250 mg per kilogram body weight of the recipient per day, preferably in the range of 5 to 40 mg per kilogram body weight per day and most preferably in the range of 5 to 10 mg per kilogram body weight per day in combination with each of the aforementioned uridine phosphorylase inhibitors of formula I. The desired dose is preferably presented as two, three, four, five, six or more sub-doses administered at appropriate intervals throught the day. These sub-doses may be administered in unit dosage forms, for example, containing 10 to 1500 mg, preferably 20 to 1000 mg, and most preferably 50 to 700 mg of active ingredient per unit dosage form.

Experiments with 3'-azido-3'-deoxythymidine(zidovudine) suggest that a dose should be administered to achieve peak plasma concentrations of the active compound of from

about 1 to about 75 uM(the abbreviation uM is used herein as micromolar), preferably about 2 to 50 uM, most preferably about 3 to about 30 uM. This may be achieved, for example, by the intravenous injection of a 0.1 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 1 to about 100 mg/kg of the active ingredient(the abbreviation "mg/kg" is well understood by one of ordinary skill in the art). Desirable blood levels may be maintained by a continuous infusion to provide about 0.01 to about 5.0 mg/kg/hour or by intermittent infusions containing about 0.4 to about 15 mg/kg of the active ingredient.

The antineoplastic pyrimidine nucleosides of the present invention are those which are known in the art and are administered according to procedures known by one skilled in the art of treating antineoplastic disease. Particularly preferred antineoplastic pyrimidine nucleosides used in accordance with the present invention include but are not limited to: 5-fluoro-2'-deoxyuridine, 5-fluorouridine, 5-fluorouracil, 5-fluoro-2'-deoxyuridine(FdUrd), 5-trifluoromethyldeoxyuridine(TFT), and 5-bromovinyldeoxyuridine(BVdU)). The antineoplastic pyrimidine nucleosides of the present invention are readily available to the skilled practicioner in the art.

The uridine phosphorylase inhibitor of formula I may be administered in a dosage in the range of 1 to 300 mg per kilogram body weight of the recipient per day, preferably in the range of 3 to 100 mg per kilogram body weight per day, most preferably in the range of 5 to 30 mg per kilogram body weight per day in combination with zidovudine or the antiviral pyrimidine nucleoside analogs or antineoplastic pyrimidine nucleosides described hereinbefore. Unless otherwise indicated, all weights of active ingredients are calculated as the parent free base compound of formula I; for salts thereof the figures would be increased proportionally.

The desired dose is preferably presented as one, two or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms for example containing 1 to 200 mg, preferably 10 to 200 mg, most preferably 10 to 100 mg of a compound of formula I.

Zidovudine and the uridine phosphorylase inhibitor are employed in an appropriate ratio whereby the above-mentioned toxic effects of zidovudine are reduced or obviated

without significant reduction of the therapeutic effect of zidovudine or the antiviral pyrimidine nucleosides.
In a similar manner to that described above for zidovudine, other antiviral pyrimidine nucleosides hereinbefore described, are used in combination with the uridine phosphorylase inhibitor to reduce the toxic effects of the antiviral pyrimidine nucleosides without significant reduction of the therapeutic effect of the antiviral pyrimidine nucleosides.

The antineoplastic pyrimidine nucleosides described hereinbefore and the uridine phosphorylase inhibitor are employed in an appropriate ratio whereby the above-mentioned antitumor effects of the antineoplastic pyrimidine nucleoside are enhanced or increased.

Zidovudine and the uridine phosphorylase inhibitor are preferably administered in a pharmaceutical formulation, either in a single pharmaceutical formulation containing both components or in separate pharmaceutical formulation each containing one of the components of the combinations.

The present invention thus includes as a further feature a pharmaceutical formulation comprising a uridine phosphorylase inhibitor of formula I optionally in combination with zidovudine together with at least one pharmaceutically acceptable carrier or excipient.

Each carrier must be "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Formulations include those adapted for oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Formulations of the present invention adapted for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethylcellulose), lubricant, inert diluent, preservative, disintegrant (e.g., sodium starch glycollate, cross-linked povidone, cross-linked sodium carboxymethylcellulose) surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile.

Formulations for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Compositions for transdermal administration may be delivered by passive diffusion or by electrically-assisted transport, for example, iontophoresis (see, for example, Pharmaceutical Research 3(6), 318, (1986)) and may take the form of an optionally buffered aqueous solution of a compound of formula I.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulation for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

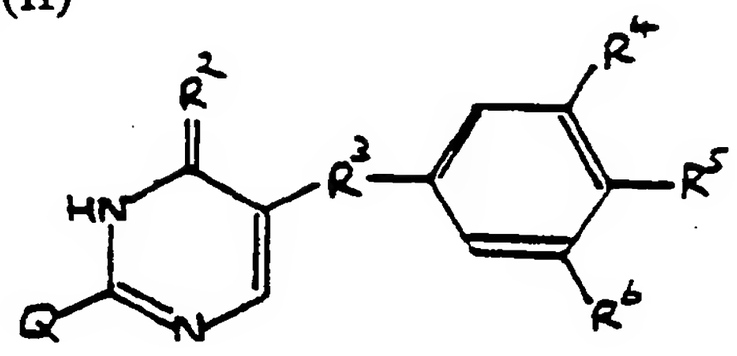
Formulations for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

Zidovudine is 3'-azido-3'-deoxythymidine(AZT) and is commercially available under the tradename RETROVIR® from Burroughs Wellcome Co., Research Triangle Park, North Carolina, USA. It is an antiviral compound active against human immunodeficiency virus(HIV) and is approved for the treatment of HIV infection in both children and adults. The preparation of zidovudine has been disclosed(Horowitz J.P. et al., J. Org. Chem. 29: 2076(1964) and Glinski R.P. et al., ibid. 38: 4299(1973)) and its synthesis and use in the treatment of AIDS and AIDS-related complex has been disclosed in U.S. Patent No. 4,724,232(1988) which is incorporated in its entirety herein by reference. Zidovudine is well known in the art.

Compounds of formula (I) may be prepared by hydrolysis of the corresponding compound of formula (II)

(II)



wherein R^2 to R^6 are as hereinbefore defined and Q is NH_2, OR^{13} or SR^{13} wherein R^{13} is C_{1-6} straight or branched chain alkyl group to give a compound of formula (I) where R^1 is H, and thereafter optionally converted to a compound of formula (I) wherein R^1 is other than H.

When Q is SH, the compound of formula (II) may exist in tautomeric form.

The hydrolysis of a compound of formula (II) may suitably be carried out with inorganic or organic acids (for example glacial acetic acid/aqueous chloroacetic acid, 20% hydrochloric acid/aqueous sodium nitrite or sulphuric acid), with an aqueous alkali (for example 20% sodium hydroxide), or when Q is SH and the compound is in the tautomeric form, with an organic peroxide and an organic alcohol (for example hydrogen peroxide/tert-butanol), and at a temperature of 0-250°C and preferably 20-150°C (for example the reflux temperature).

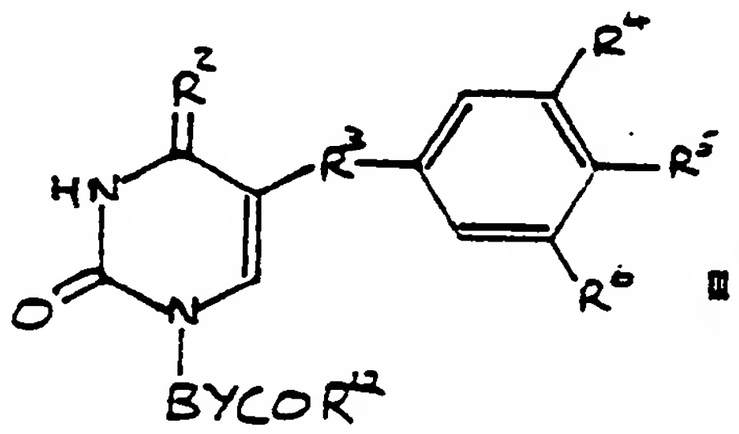
The conversion to a compound of formula (I) wherein R^1 is other than H may be carried out by the reaction of a compound of formula (I) where R^1 is H with a silylating agent, for example, trimethylsilyl chloride, bis(trimethylsilyl)acetamide or hexamethyldisilazane either neat or in a suitable inert solvent, for example, 1,2-dichloroethane or dichloromethane at a temperature of between 0-150° C (preferably the reflux temperature) and then further reacting the intermediate generated with XR^1(wherein X is a leaving group, for example, halogen(preferably chloro or bromo) or acyloxy, and R^1 is as defined hereinbefore other than H) at a temperature of between 0-150° C (preferably at ambient temperature). A glycosidic bond forming

catalyst(e.g., trifluoromethane sulfonic acid, 4-toluenesulfonic acid, stannic chloride or triethylamine) can be added to facilitate the rate of reaction.

Alternatively, the conversion can be effected by reacting an excess of the compound of formula (I) where R^1 is H with XR^1(wherein X is a leaving group, for example, halogen(preferably chloro or bromo) or acyloxy, and R^1 is as defined hereinbefore other than H) in an inert organic solvent(e.g., DMF, DMSO) in the presence of a base(e.g., K_2CO_3, $NaHCO_3$ or NaH) at a temperature of between 0-150° C.

Compounds of formula XR^1 can be obtained by methods well-known to those skilled in the art.

Compounds of formula I wherein R^1 contains at least one -OH or $-NH_2$ moiety can be converted by the hydrolysis of a compound of formula III



III

wherein R^2, R^3, R^4, R^5, and R^6 are as hereinbefore defined, B is that portion of R^1 other than -OH or $-NH_2$, Y is O or NH and R^{12} is C1-6 straight or branched-chain alkyl, C_6H_5 or substituted aryl, with ammonia gas or an organic amine(for example, methylamine, dimethylamine). The reaction will generally be carried out with stirring in an organic solvent such as an organic alcohol, e.g., methanol or ethanol, at a temperature between 0-150° C., preferably ambient temperature; or by treatment with a metal alkoxide(e.g., sodium ethoxide) in water or alcohol; or by treatment with an inorganic base(e.g., a metal hydroxide such as NaOH or KOH) in H_2O or alkanol solvent(e.g., methanol); or by treatment with alcohol(e.g., ethanol) in the presence of potassium carbonate; or by hydrolysis with aqueous acid(e.g., 1N hydrochloric acid) optionally with an organic cosolvent such as tetrahydrofuran. The reaction temperature may conveniently be between 0-150° C. and preferably at ambient temperature.

Alternatively, the target hydroxy compounds may be formed from the intermediate O-benzyl ethers by treatment with hydrogen in an organic alcohol solvent(e.g., ethanol) in the presence of a catalyst(e.g., palladium).

Alternatively, the target hydroxy compounds may be formed from the O-trimethylsilyl ether intermediate by hydrolysis with neat or aqueous organic alcohol(e.g., ethanol) under acidic or neutral conditions.

Compounds of formula III can be prepared by reacting a compound of formula (I) where R^1 is H with $XBYCOR^{12}$(wherein X, B, Y and R^{12} are as previously defined) by the methods described herein for the preparation of compounds of formula I by replacing XR^1 with $XBYCOR^{12}$.

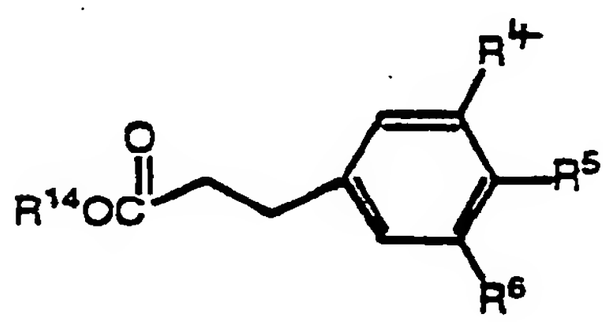
Compounds of formula $XBYCOR^{12}$ can be obtained by methods well-known to those skilled in the art.

It will be appreciated by one of ordinary skill in the art that the esters depicted in formula III are prodrugs as defined hereinbefore and thereby constitute a further aspect of this invention.

The compounds of formula III are also hydrolysed by any of the standard methods of hydrolysis of carboxylic acid esters such as those described in, e.g., J. March, Advanced Organic Chemistry, 2nd edit., 349-353, McGraw-Hill, N.Y., 1977.

Compounds of formula (II) can be prepared by reacting an ester as depicted by formula

(IV)



(IV)

(wherein R^4, R^5 and R^6 are as defined hereinbefore and R^{14} is C_{1-6} straight or branched chain alkyl; preferably R^{14} is ethyl) dissolved in a suitable inert solvent such as tetrahydrofuran with a non-nucleophilic base(e.g., lithium diisopropylamide, sodium, sodium hydride or potassium tert-butoxide) at a temperature of -100-25° C.(preferably -78° C). The resulting anionic intermediate is then reacted with an alkyl formate(preferably ethyl formate) at a temperature of -78-25° C(preferably -30° C). The resulting anionic salt of the alpha-formyl ester is then reacted with a urea derivative, such as thiourea, guanidine, O-alkylisourea or S-alkylisothiourea at a temperature of -78-25° C.

Alternatively, the intermediate anionic salts may be O-alkylated using an alkylating agent(e.g., methyl iodide or dimethyl sulfate) to generate an enol ether which is reacted with thiourea, guanidine, O-alkylisourea or S-alkylisothiourea.

Compounds of formula (IV) can be obtained by methods well-known to those skilled in the art.

The following Examples illustrate the present invention and should not be construed as limiting thereof.

Example 1
Preparation of 1-((2-hydroxyethoxy)methyl)-5-(3-propoxybenzyl)uracil

A. Preparation of (E)-ethyl 3-(3-hydroxyphenyl)-2-propenoate

This compound was prepared by the following modified method of Stodola, J. Org. Chem., 1964, 29, 2490. A solution of (E)-3-(3-hydroxyphenyl)-2-propenoic acid (Aldrich) (100.00 g, 609 mmoles) and 1.0 M ethereal hydrochloric acid (100 ml) in absolute ethanol (1000 ml) was refluxed with stirring under nitrogen for 48 hours. The ethanol was removed in vacuo, and the residue dissolved in ethyl acetate (600 ml) and washed with a saturated aqueous sodium bicarbonate solution (2 x 400 ml). The washes were back-extracted with ethyl acetate (2 x 100 ml) and the combined extracts washed with water (300 ml) and brine (400 ml), dried over anhydrous sodium sulfate and filtered.

The filtrate was evaporated in vacuo to give 113.55 g (97%) of ethyl 3-(3-hydroxyphenyl)-2-propenoate as a brown waxy solid, which was used without further purification; tlc, dichloromethane.

B. Preparation of ethyl 3-(3-hydroxyphenyl)propanoate

This compound was prepared by the following modification of the previously reported method of J.M. Bruce, D. Creed and H. Dawes, J. Chem. Soc. C., 1971, 3749-3756.

A mixture of (E)-ethyl 3-(3-hydroxyphenyl)-2-propenoate (30.0 g, 156 mmoles), platinum oxide hydrate (0.25 g, 1.1 mmoles) and 95% ethanol (150 ml) was shaken in the presence of hydrogen at 2-3 atmospheres for 18 hours. The catalyst was removed by filtration through Celite, and the filtrate was evaporated in vacuo to give 26.72 g (89%) of ethyl 3-(3-hydroxyphenyl)propanoate as a brown oil, which was used without further purification; tlc, dichloromethane.

C. Preparation of ethyl 3-(3-propoxyphenyl)propionate

A mixture of ethyl 3-(3-hydroxyphenyl)propanoate (18.0 g, 92.7 mmoles), bromopropane (11.4 g, 92.7 mmoles), potassium carbonate (20.0 g, 144.7 mmoles), potassium iodide (18.5 g, 111.4 mmoles) and acetone (300 ml) was refluxed with stirring under a calcium chloride drying tube for 48 hours. The cooled mixture was filtered, and the solids washed with diethyl ether (3 x 50 ml). The filtrate and washings were combined, and the solvents removed in vacuo. The residue was taken up in diethyl ether, washed successively with water (200 ml), 0.5 N sodium hydroxide (150 ml), water (100 ml) and brine (100 ml). The extracts were dried over anhydrous magnesium sulfate, filtered and evaporated in vacuo to give 17.1 g (78%) of ethyl 3-(3-propoxyphenyl)propionate as a brown oil. Part of the product was purified by flash chromatography on Silica Gel 60. The column was eluted with hexanes:ethyl acetate (1:1) to give an analytically pure sample.

D. Preparation of
1,2-dihydro-5-(3-propoxybenzyl)-2-thioxo-4(3H)-pyrimidinone

A solution of ethyl 3-(3-propoxyphenyl)propionate (2.00 g, 8.5 mmoles) in tetrahydrofuran (3 ml) was added to a solution of lithium diisopropylamine [This salt was prepared from diisopropylamine (1.42 ml, 10.0 mmoles) and n-butyl lithium (5 ml of a 2 M pentane solution, 10.0 mmoles)] in tetrahydrofuran (7 ml), cooled to -78°C under nitrogen. The solution was stirred for 1.5 hours while the temperature was allowed to rise to -60°C. The solution was cooled to -78°C, ethyl formate (0.8 ml, 10.0 mmoles) added, and stirring continued for 2.5 hours while the solution warmed to -30°C. After re-cooling to -78°C, thiourea (0.76 g, 10.0 mmoles) was added in one portion, and the resulting suspension allowed to warm to ambient temperature. Ethanol (15 ml) was added, and the solution was refluxed under nitrogen for 18 hours. The ethanol was removed in vacuo, and the residue was partitioned between dichloromethane:water (75 ml:125 ml). The layers were separated, and the aqueous layer was washed with additional dichloromethane (2 x 100 ml). The organic washes were combined and back-extracted with 0.5 N sodium hydroxide. The combined aqueous layers were cooled in an ice bath, and the pH was adjusted to 4 with concentrated hydrochloric acid. The light brown precipitate was collected on a filter, washed several times with water and diethyl ether, and dried under a vacuum at ambient temperature for 18 hours to give 1.24 g (53%) of 1,2-dihydro-5-(3-propoxybenzyl)-2-thioxo-4 (3H)-pyrimidinone, mp 183-185°C. Recrystallization from acetonitrile gave 0.53 g of an analytically pure sample.

E. Preparation of 5-(3-propoxybenzyl)uracil

A suspension of 1,2-dihydro-5-(3-propoxybenzyl)-2-thioxo-4(3H) -pyrimidinone (0.350 g, 1.3 mmoles) in glacial acetic acid (5 ml) and 20% aqueous chloroacetic acid (5 ml) was refluxed with stirring for 18 hours. After cooling to ambient temperature and then in an ice bath, the mixture was filtered, and the solids were washed with water and diethyl ether and dried in a

vacuum oven at 80°C for 18 hours to give 0.28 g (85%) of 5-(3-propoxybenzyl) uracil as an off-white solid, mp 247-249°C.

F. Preparation of 1-((2-acetoxyethoxy)methyl)-5-(3-propoxybenzyl)uracil · 1/2 hydrate

Bis(trimethylsilyl)acetamide (0.85 ml, 3.4 mmoles) was added to a stirred suspension of 5-(3-propoxybenzyl)uracil (0.50 g, 1.9 mmoles) in dichloroethane (20 ml) under nitrogen. The mixture was refluxed with stirring for 35 minutes, and the resultant solution cooled in an ice bath. A solution of (2-acetoxyethoxy)methyl bromide (0.327 g, 1.7 mmoles), see below for preparation, in acetonitrile (3 ml) was added to the cooled solution and the resultant solution allowed to warm to ambient temperature and stirred under nitrogen for 18 hours. The volatiles were removed in vacuo, and the residual oil introduced onto a column of Silica Gel 60 wetted with dichloromethane. The column was eluted with dichloromethane:methanol (30:1), and the fractions containing product were combined. The solvents were removed in vacuo to give 0.63 g (83%) of 1-((2-acetoxyethoxy)methyl)-5-(3-propoxybenzyl)uracil · 1/2 hydrate as a light yellow oil; tlc, dichloromethane:methanol (19 :1); uv (0.1 N hydrochloric acid + 10% methanol): l_{max} 266 nm (e. 10100); (pH 7 buffer + 10% methanol): l_{max} 266 nm (e 9500); (0.1 N sodium hydroxide + 10% methanol): l_{max} 267 nm (e 7200).

Preparation of (2-acetoxyethoxy)methyl bromide (Robins, M.I. and Hatfield, P.W., Can. J. Chem., 1982, 60, 547). Freshly distilled acetyl bromide (13.0 g, 106 mmol) was stirred magnetically with cooling in an ice bath while 7.4 g (100 mmol) of 1,3-dioxolane was added slowly. A rapid exothermic reaction occurred giving quantitative conversion to the title compound (as judged by ^1H NMR). Vacuum distillation of this material gave 17.4 g (88%) of product, bp 58-60°C/0.1 Torr.

G. Preparation of 1-((2-hydroxyethoxy)methyl)-5-(3-propoxybenzyl)uracil · 1/4 hydrate

A solution of 0.30 g (0.8 mmoles) of 1-((2-acetoxyethoxy)methyl)-5-(3-propoxybenzyl)uracil in methanol (250 ml) saturated with ammonia gas was stirred in a stoppered flask for 18 hours at ambient temperature. The methanol was removed in vacuo, and the residue was recrystallized from dichloromethane / hexane:one drop water to give 0.19 g (70%) of 1-((2-hydroxy-ethoxy)methyl)-5-(3-propoxybenzyl)uracil · 1/4 hydrate as a white solid m.p. 85-87°C; uv (0.1 N hydrochloric acid + 10% methanol): l_{max} 266 nm (e 9800); (0.1 N sodium hydroxide + 10% methanol): l_{max} 265 nm (e 10900); NMR (DMSO-d_6): d 7.62 (s, 1H, H-6), 6.94 (m, 4H, ArH), 5.06 (s, 2H, NCH_2O), 4.68 (s, 1H, OH), 3.86 (t, 2H, J=6.5 Hz, OCH_2), 3.47 (s, 6H, CH_2Ar and $(CH_2)_2$), 1.71 (dq, 2H, J=6.5 Hz and 7.4 Hz, CCH_2C), 0.94 (t, 3H, J=7.4 Hz, CH_3); ms: m/e 335.
Anal. Calcd. for $C_{17}H_{22}N_2O_5 \cdot 1/4\ H_2O$: C, 60.25; H, 6.69; N, 8.27.
Found: C, 60.23; H, 6.70; N, 8.21.

Example 2
Preparation of
1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-propoxybenzyl)uracil

A) Preparation of
2-((1,2,3,4-tetrahydro-2,4-dioxo-5-(3-propoxybenzyl)-1-pyrimidinyl)methoxy)-1,3-propanediyl diacetate

This compound was prepared in an analogous manner to that of Example 1F with the replacement of 0.327 g of (2-acetoxyethoxy) methyl bromide in Example 1F with 0.51 g of (2-acetoxy-(1-acetoxy-methyl)ethoxy)methyl bromide (see below for preparation). The chromatography fractions were spin evaporated in vacuo to give 0.83 g (98%) of 2-((1,2,3,4-tetrahydro-2,4-dioxo-5-(3-propoxybenzyl)-1-pyrimidinyl)methoxy)-1,3-propane-diyl diacetate as a clear oil; tlc, dichloro-methane:methanol (19:1).

(2-acetoxy-(1-acetoxy-methyl)ethoxy)methyl bromide

This compound was made by the same method as that described for 2-(bromomethoxy)-1,3-propanediyl dibenzoate, referred to in Example 4A, with the replacement of sodium benzoate with an equimolar amount of sodium acetate.

B. Preparation of 1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-propoxybenzyl) uracil

This compound was prepared in an analogous manner to that of Example 1G with the replacement of 0.30 g of 1-((2-acetoxyethoxy)methyl)-5- (3-propoxybenzyl) uracil with 0.73 g of 2-((1,2,3,4-tetrahydro-2,4-dioxo-5-(3-propoxybenzyl)-1-pyrimidinyl) methoxy)-1,3-propanediyl diacetate. The methanol was removed in vacuo, and the residue was chromatographed on silica Gel 60, eluting with dichloromethane: methanol (19:1) to give 0.44 g of a waxy solid which was washed with water to give 0.14 g (24%) of 1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-propoxybenzyl) uracil as a white solid, mp 101-102°C.

Example 3

Preparation of 1-((2-hydroxyethoxy)methyl)-5-(3-phenoxybenzyl)uracil

A. Preparation of (E)-3-(3-phenoxyphenyl)-2-propenoic acid

A solution of 3-phenoxybenzaldehyde (Aldrich) (25.0 g, 126 mmol), malonic acid (26.2 g, 252 mmol) and piperidine (2.0 ml, 20 mmol) in pyridine (50 ml) was stirred in an oil bath heated at 90°C for 18 h. After cooling to ambient temperature, the solution was poured into cold water (1 L). The pH of the aqueous mixture was adjusted to pH 2 with concentrated hydrochloric acid. The solids which formed were collected by suction filtration, washed with water, and recrystallized from acetonitrile/water to give 24.18 g (80%) of (E)-3-(3-phenoxyphenyl)-2-propenoic acid as a white solid: mp 111-113°C; tlc, methanol: dichloromethane (1:19).

B. Preparation of (E)-ethyl 3-(3-phenoxy)phenyl-2-propenoate

A solution of (E)-3-(3-phenoxyphenyl)-2-propenoic acid (14.51 g, 60.4 mmoles) and 1.0 M ethereal hydrochloric acid (40 ml) in absolute ethanol (150 ml) was refluxed with stirring under nitrogen for 24 hours. The ethanol was removed in vacuo and the residue taken up in ethyl acetate (150 ml) and washed with a saturated aqueous sodium bicarbonate solution (2 x 75 ml). The washes were back-extracted with ethyl acetate (50 ml) and the combined extracts washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated in vacuo to give 15.31 g (94%) of (E)-ethyl 3-(3-phenoxy)-2-propenoate as a yellow oil, which was used without further purification.

C. Preparation of ethyl 3-(3-phenoxyphenyl)propanoate

A mixture of (E)-ethyl 3-(3-phenoxyphenyl)-2-propenoate (15.2 g, 56.7 mmoles), platinum oxide hydrate (0.10 g, 0.44 mmoles) and 95% ethanol (60 ml) was shaken in the presence of hydrogen at 2-3 atmospheres for 18 hours. The catalyst was removed by filtration through Celite and the ethanol removed from the filtrate in vacuo to give 13.87 g (90%) of ethyl 3-(3-phenoxyphenyl) propanoate as an orange oil, which was used without further purification; tlc, dichloromethane : hexane (1:1).

D. Preparation of 1,2-dihydro-5-(3-phenoxybenzyl)-2-thioxo-4(3H)-pyrimidinone

A solution of ethyl 3-(3-phenoxyphenyl)propanoate (10.90 g, 33.0 mmoles) and ethyl formate (5.33 g, 72.0 mmoles) in diethyl ether (75 ml) was added dropwise with stirring to a solution of potassium tert-butoxide (1 M in tetrahydrofuran, 81.4 ml, 81.4 mmoles) in diethyl ether (225 ml) cooled in an ice bath under nitrogen. The solution was stirred at ambient temperature for 18 hours, and the solvent was removed in vacuo. The residue was treated with 2-propanol (100 ml) and thiourea (6.18 g, 66.0 mmoles) and the resulting

mixture was refluxed for 5 hours under nitrogen. The solvent was removed in vacuo, and the solid residue was washed with cold diethyl ether, dissolved in cold water, and the pH was adjusted to 4 with glacial acetic acid. The beige precipitate was collected on a filter, washed several times with water and diethyl ether, and dried under a vacuum at ambient temperature for 18 hours to give 7.97 g (78%) of 1,2-dihydro-5-(3-phenoxybenzyl)-2-thioxo-4 (3H)-pyrimidinone, mp 195-197°C (dec.). Recrystallization of 0.85 g from acetonitrile gave 0.36 g of an analytically pure sample; tlc, dichloromethane : methanol (19:1); uv (0.1 N hydrochloric acid + 10% methanol): l 276 nm (e 24400); (pH 7 buffer + 10% methanol): l 275 nm (e 22500); (0.1 N sodium hydroxide + 10% methanol): l 262 nm (e 17700); sh 307 nm (e 9500).

E. Preparation of 5-(3-phenoxybenzyl) uracil

A suspension of 1,2-dihydro-5-(3-phenoxybenzyl)-2-thioxo-4(3H)-pyrimidinone (7.97 g, 25.7 mmoles) in glacial acetic acid (140 ml) and 20% aqueous chloroacetic acid (140 ml) was refluxed with stirring for 6 hours. After cooling to ambient temperature and then in an ice bath, the mixture was filtered, and the solids were washed with water and diethyl ether and dried in a vacuum oven at 70°C for 18 hours to give 6.46 g (85%) of 5-(3-phenoxybenzyl)uracil as an off-white solid, mp 281-283°C. Recrystallization of 0.410 g from acetic acid/water gave 0.208 g of an analytically pure sample; tlc, dichloro-methane : methanol (19 : 1), uv (0.1 N hydrochloric acid + 10% methanol): l 268 nm (e 24000), sh 296 nm (e 11600); (pH 7 buffer + 10% methanol): l 267 nm (e 16600), sh 300 nm (e 6500); (0.1 N sodium hydroxide + 10% methanol): l 279 nm (e 8300), sh 291 nm (e 7500).

F. Preparation of 1-((2-acetoxyethoxy)methyl)-5-(3-phenoxybenzyl)uracil 1/4 hydrate

Bis(trimethylsilyl)acetamide (8.24 ml, 32.5 mmoles) was added to a stirred suspension of 5-(3-phenoxybenzyl)uracil (5.435 g, 18.5 mmoles) in 1,2-dichloroethane (95 ml) under nitrogen. The mixture was refluxed with

stirring for 3 hours, the heat removed and the solution that formed cooled in an ice bath. A solution of (2-acetoxyethoxy)methyl bromide (3.15 g, 16.0 mmoles) in acetonitrile (15 ml) was added to the cooled solution, the resulting solution allowed to warm to ambient temperature and stirred under nitrogen for 18 hours. The solvents were removed in vacuo and the residual oil introduced onto a column of Silica Gel 60 wetted with dichloromethane. The column was eluted with dichloromethane : 2-propanol (100 : 1), and the fractions containing product were combined. The solvents were removed in vacuo, and the residue was dissolved in dichloromethane (150 ml) and washed with water (3 X 75 ml) and brine. The dichloromethane solution was dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo to give 5.301 g (80%) of 1-((2-acetoxyethoxy)methyl)-5-(3-propoxy-benzyl)uracil _1/4 hydrate as a clear oil; tlc, dichloromethane : methanol (19 :1); uv (0.1 N hydrochloric acid + 10% methanol): l 266 nm (e 11800); (pH 7 buffer + 10% methanol): l 266 nm (e 10800); (0.1 N sodium hydroxide + 10% methanol): l 265 nm (e 8800).

G. Preparation of 1-((2-hydroxyethoxy)methyl)-5-(3-phenoxybenzyl)uracil

A solution of 8.40 g (20.3 mmoles) of 1-((2-acetoxyethoxy)methyl)-5-(3-phen-oxybenzyl)uracil in methanol (300 ml) saturated with ammonia gas was stirred in a stoppered flask for 24 hours at ambient temperature. The methanol was removed in vacuo, and the residue was washed with water and diethyl ether and dried in a vacuum oven at 80°C to give 5.532 g (74 %) of 1-((2-hydroxy-ethoxy)methyl)-5-(3-phenoxybenzyl)uracil as a white solid, mp 93-95°C; uv (0.1 N hydrochloric acid + 10% methanol): l 266 nm (e 12000); (pH 7 buffer + 10% methanol): l 266 nm (e 11800); (0.1 N sodium hydroxide + 10% methanol): l 265 nm (e 8700); NMR (DMSO-d_6): d 11.40 (s, 1H, NH), 7:65 (s, 1H, H-6), 6.94 (m, 9H, ArH), 5.09 (s, 2H, NCH_2O), 4.68 (s, 1H, OH), 3.49 (s, 6H, CH_2Ar and $(CH_2)_2$) ; ms: m/e 369.
Anal. Calcd. for $C_{20}H_{20}N_2O_5$: C,65.20; H, 5.47; N, 7.61.
Found: C, 65.25; H, 5.51; N, 7.62.

Example 4

Preparation of 1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)5-(3 phenoxybenzyl)uracil

A. Preparation of 2-((1,2,3,4-tetrahydro-2,4-dioxo-5-(3-phenoxybenzyl)-1-pyrimidinyl)methoxy)-1,3-propanediyl dibenzoate

This compound was prepared in an analogous manner to that of Example 3F with 9.10 g of 2-(bromomethoxy)-1,3-propanediyl dibenzoate (see below for preparation). The chromatography fractions were spin evaporated in vacuo to give 10.09 g of 2-((1,2,3,4-tetrahydro-2,4-dioxo-5-(3-phenoxybenzyl)-1-pyrimidinyl)methoxy)-1,3-propanediyl dibenzoate as a white solid, which was used without further purification.

Preparation of 2-(bromomethoxy)-1,3-propanediyl dibenzoate

This compound was made by the following method of Beauchamp. et al., J. Med. Chem., 1988, 31, 144.

1,3-Dichloro-2-(methoxymethoxy)propane. To a solution of 500 g (3.88 mol) of 1,3-dichloro-2-propanol (2), 780 mL of chloroform, and 780 mL of dimethoxymethane was added 330 g (2.32 mol) of phosphorus pentoxide, portion wise, with vigorous stirring, with the temperature maintained at 40-45°C. The mixture was then stirred at ambient temperature for 18 h. The supernatant was decanted and washed once with water, once with 10% aqueous sodium bicarbonate, and once more with water. The organic layer was dried (sodium sulfate) and evaporate in vacuo to give 569 g (85%) of a pale amber liquid, which was of sufficient purity for use.

2-(Methoxymethoxy)-1,3-propanediyl dibenzoate. A mixture of 181.1 g (1.04 mol) of 1,3-dichloro-2-(methoxymethoxy)propane, 3453.0 g (3.14 mol) of sodium benzoate, 20 mL (0.1 mol) of 15-crown-5 ether, and 2.5 L of dimethylformamide was refluxed with stirring for 2 days. The cooled reaction mixture was filtered and the precipitate washed with ether. The combined washings and filtrate were flash evaporated, and the residue was triturated with

ether. the ethereal extracts were washed with water, dried (sodium sulfate), and evaporated to yield 341 g (95%) of a dark brown oil.

2-(Acetoxymethoxy)-1,3-propanediyl dibenzoate. A solution of 143 g (0.415 mol) of 2-(Methoxymethoxy)-1,3-propanediyl dibenzoate in 55 mL (0.581 mol) of acetic anhydride and 14.3 mL (0.12 mol) of boron trifluoride etherate was stirred at 0°C for 2 h. The solution was poured into 800 mL of ice and water containing 60 g of sodium bicarbonate. The oily mixture was extracted with three 600-mL portions of ether. The ethereal extracts were washed once with 10% aqueous sodium bicarbonate solution and twice with water and dried over sodium sulfate. The solvent was removed in vacuo to give 154 g (99%) of 2-(acetoxymethoxy)-1,3-propanediyl dibenzoate, which was of sufficient purity for further use.

2-(Bromomethoxy)-1,3-propanediyl dibenzoate. A mixture of 15 g (0.04 mol) of 2-(acetoxymethoxy)-1,3-propanediyl dibenzoate, 70 mL of dry dichloromethane, and 17 mL of bromotrimethylsilane was gently refluxed for 18 h. The solution was evaporated in vacuo to give the target compound, 2-(Bromomethoxy)-1,3-propanediyl dibenzoate, as a light amber oil in quantitative yield.

B. 1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-phenoxybenzyl)uracil

This compound was prepared in an analogous manner to that of Example 3G with the replacement of 8.40 g of 1-((2-acetoxyethoxy)methyl)-5-(3-phenoxybenzyl)uracil and 300 mL of methanol saturated with ammonia gas in Example 3G with 9.25 g of 2-((1,2,3,4-tetrahydro-2,4-dioxo-5-(3-phenoxybenzyl)-1-pyrimidinyl)methoxy) -1, 3-propanediyl dibenzoate and 200 mL of 40% aqueous methyl amine, respectively. The mixture was sealed in a bomb and heated at 80°C for 5 days. Since the reaction was incomplete, the solvent was removed in vacuo, the residue was taken up in MeOH (100 mL), and sodium methoxide (0.70 g, 0.013 mmoles) was added. The mixture was refluxed for 18 hours, cooled in an ice bath, and neutralized with 1.0 M ethereal hydrochloric acid. The white precipitate which formed was collected by filtration, washed with water and diethyl ether, recrystallized from methanol,

and dried in vacuum oven at 80°C to give 1.921 g (32%) of 1-((2-hydroxy-1-(hydroxymethyl)-ethoxy)methyl)-5-(3-phenoxybenzyl)uracil as a white solid, mp 139-141°C; uv (0.1 N hydrochloric acid + 10% methanol): l 266 nm (e 10800); (pH 7 buffer + 10% methanol): l 266 nm (e 10100); (0.1 N sodium hydroxide + 10% methanol): l 265 nm (8100): NMR (DMSO-d_6): d 11.35 (s, 1H, NH, 7.67 (s, 1H, H-6), 711 (m, 9H, ArH), 5.17 (s, 2H, NCH_2O), 4.62 (t, 2H, OH), 3.58 (s, 2H, CH_2Ar), 3.42 (m, 5H, CH and CH_2OH); ms: m/e 399.

Anal. Calcd. for $C_{21}H_{22}N_2O_6$: C, 63.30; H, 5.57; N, 7.03.
Found: C, 63.28; H, 5.60; N, 7.06.

Example 5

Preparation of 1-((2-hydroxyethoxy)methyl)-5-(3-(3-fluoropropoxy)benzyl)uracil

A. Preparation of ethyl 3-(3-(3-fluoropropoxy)phenyl)-2-propanoate

A mixture of ethyl 3-(3-hydroxyphenyl)-2-propanoate (7.77 g, 40.0 mmoles), 1-bromo-3-fluoropropane (7.1 g, 50.4 mmoles), potassium carbonate (8.3 g, 60.0 mmoles), potassium iodide (8.3 g, 50.0 mmoles) and acetone (150 ml) was refluxed with stirring under a calcium chloride drying tube for 48 hours. The mixture was recharged with additional potassium carbonate (8.0 g, 57.9 mmoles) and refluxed for 18 hours. The cooled mixture was filtered and the solids washed with ethyl acetate (3 x 50 ml). The filtrate and washings were combined and the solvents removed in vacuo. The residue was purified by flash chromatography on Silica Gel 60 eluting with hexanes : ethyl acetate (98 : 2) to give 8.95 g (88%) of ethyl 3-(3-(3-fluoropropoxy)phenyl)-2-propanoate as a pale yellow oil.

B. Preparation of 1,2-dihydro-5-(3-(3-fluoropropoxybenzyl)-2-thioxo-4(3H)-pyrimidinone

A solution of ethyl 3-(3-(3-fluoropropoxy)phenyl)-2-propanoate (1.83 g, 7.2 mmoles) in tetrahydrofuran (3 ml) was added to a solution of lithium diisopropylamine freshly prepared from diisopropylamine (1.2 ml, 8.6 mmoles) and n-butyl lithium (3.4 ml of a 2.5 M hexane solution, 8.6 mmoles), in

tetrahydrofuran (7 ml), cooled to -78°C under nitrogen. The solution was stirred for 2.0 hours while the temperature was allowed to rise to -55°C. The solution was cooled to -78°C, ethyl formate (0.68 ml, 8.6 mmoles) added, and stirring continued for 2.0 hours while the solution warmed to -60°C. After recooling to -78°C, thiourea (0.65 g, 8.6 mmoles) was added in one portion and the resulting suspension allowed to warm to ambient temperature. Ethanol (30 ml) was added, and the solution was refluxed under nitrogen for 6 hours. The ethanol was removed in vacuo, and the residue was partitioned between dichloromethane : water (50 ml : 100 ml). The layers were separated, and the aqueous layer was washed with additional dichloromethane (2 x 50 ml). The aqueous solution was cooled in an ice bath, and the pH was adjusted to 3 with concentrated hydrochloric acid. The precipitate was collected on a filter, washed several times with water and diethyl ether, and dried under a vacuum at ambient temperature for 18 hours to give 0.84 g (39%) of crude 1,2-dihydro-5-(3-(3-fluoropropoxy)benzyl)-2-thioxo-4(3H)-pyrimidinone which was used in the next step without further purification. Recrystallization of 0.33 g from acetonitrile gave 0.17 g of an analytically pure sample, mp 166-167°C; tlc, dichloromethane: methanol (19 : 1).

C. Preparation of 5-(3-(3-fluoropropoxy)benzyl)uracil

A suspension of 1,2-dihydro-5-(3-(3-fluoropropoxy)benzyl)-2-thioxo-4(3H)-pyrimidinone (0.50 g, 1.6 mmoles) in glacial acetic acid (8 ml) and 20% aqueous chloroacetic acid (8 ml) was refluxed with stirring for 6 hours. After cooling to ambient temperature and then in an ice bath, the mixture was filtered, and the solids were washed with water and diethyl ether and dried in a vacuum oven at 80°C for 18 hours to give 0.392 g (88%) of 5-(3-(3-fluoropropoxy)benzyl)uracil as a white solid, mp = 240-242°C; tlc, dichloromethane : methanol (19 : 1).

D. Preparation of 1-((2-acetoxyethoxy)methyl)-5-(3-(3-fluoropropoxy)benzyl)uracil

Bis(trimethylsilyl)acetamide (2.05 ml, 8.4 mmoles) was added to a stirred suspension of 5-(3-(3-fluoropropoxy)benzyl)uracil (1.30 g, 4.7 mmoles) in

dichloroethane (45 ml) under nitrogen. The mixture was refluxed with stirring for 35 minutes, the heat removed, and the solution which formed cooled in an ice bath. A solution of (2-acetoxyethoxy)methyl bromide (0.81 g, 4.1 mmoles) in acetonitrile (5 ml) was added to the cooled solution and the resulting solution allowed to warm to ambient temperature and stirred under nitrogen for 18 hours. The solvents were removed in vacuo and the residual oil introduced onto a column of Silica Gel 60 wetted with dichloromethane. The column was eluted with dichloromethane : methanol (99:1), and the fractions containing product were combined and evaporated in vacuo. The residue was dissolved in ethyl acetate, washed with water (2 x 50 ml) and brine (50 ml), dried over anhydrous sodium sulfate, filtered and evaporated in vacuo to give 1.10 g (59%) of 1-((2-acetoxyethoxy)methyl)-5-(3-(3-fluoropropoxy)benzyl)uracil as a clear oil; tlc, dichloromethane : methanol (19:1).

E. Preparation of
1-((2-hydroxyethoxy)methyl)-5-(3-(3-fluoropropoxy)benzyl)uracil

A solution of 1-((2-acetoxyethoxy)methyl)-5-(3-(3-fluoropropoxy)benzyl) uracil (1.05 g, 2.7 mmoles) in methanol (100 ml) saturated with ammonia gas was stirred in a stoppered flask for 18 hours at ambient temperature. The methanol was removed in vacuo, and the residue was recrystallized from 2-propanol : hexane and dried in a vacuum oven at 48°C to give 0.725 g (77 %) of 1-((2-hydroxy-ethoxy)methyl)-5-(3-(3-fluoropropoxy)- benzyl)uracil as a white solid, mp 78-82°C; uv (0.1 N hydrochloric acid + 10% methanol): l 266 nm (e 11600); (pH 7 buffer + 10% methanol): l 266 nm (e 11500); (0.1 N sodium hydroxide + 10% methanol): l 268 nm (e 7600); NMR (DMSO-d_6): d 11.40 (s, 1H, NH), 7.65 (s, 1H, H-6), 6.94 (m, 4H, ArH), 5.09 (s, 2H, NCH_2O), 4.68 (s, 1H, OH), 4.72 (t, 1H, CHF), 4.49 (t, 1H, CHF), 4.03 (t, 2H, OCH_2), 3.49 (s, 6H, CH_2Ar and $(CH_2)_2$), 2.10 (m, 2H, $CH_2CH_2CH_2$) ; ms: m/e 353.
Anal. Calcd. for $C_{17}H_{21}N_2O_5F$: C,57.94; H, 6.01; N, 7.95.
Found: C, 58.03; H, 5.99; N, 7.89.

Example 6

Preparation of 1-((2-hydroxyethoxy)methyl)-5-(3-sec-butoxybenzyl)uracil

A. Preparation of ethyl 3-(3-sec-butoxyphenyl)-2-propanoate

A mixture of ethyl 3-(3-hydroxyphenyl)-2-propanoate (9.0 g, 46.4 mmoles), 2-bromobutane (10.0 ml, 61.0 mmoles), potassium carbonate (17.0 g, 123.0 mmoles), potassium iodide (10.0 g, 60.2 mmoles) and acetone (200 ml) was refluxed with stirring under a calcium chloride drying tube for 5 days. The mixture was recharged with additional potassium carbonate (8.3 g, 60.0 mmoles) and 2-bromobutane (10.0 ml, 61.0 mmoles) and refluxed for 48 hours. The cooled mixture was filtered and the solids washed with ethyl acetate (3 x 75 ml). The filtrate and washings were combined and the solvents removed in vacuo. The residue was purified by flash chromatography on Silica Gel 60 eluting with hexanes : ethyl acetate (98:2) to give 8.93 g (77%) of ethyl 3-(3-sec-butoxyphenyl)-2-propanoate as a yellow oil.

B. Preparation of
1,2-dihydro-5-(3-sec-butoxybenzyl)-2-thioxo-4(3H)-pyrimidinone

A solution of ethyl 3-(3-sec-butoxyphenyl)-2-propanoate (4.0 g, 16.0 mmoles) in tetrahydrofuran (7 ml) was added to a solution of lithium diisopropylamine freshly prepared from diisopropylamine (2.75 ml, 19.4 mmoles) and n-butyl lithium (7.75 ml of a 2.5 M hexane solution, 19.4 mmoles), in tetrahydrofuran (15 ml), cooled to -78°C under nitrogen. The solution was stirred for 1.5 hours while the temperature was allowed to rise to -65°C. The solution was cooled to -78°C, ethyl formate (1.6 ml, 20.0 mmoles) added, and stirring continued for 2.0 hours while the solution warmed to -60°C. After recooling to -78°C, thiourea (1.47 g, 19.4 mmoles) was added in one portion and the resulting suspension allowed to warm to ambient temperature. Ethanol (15 ml) was added, and the solution was refluxed under nitrogen for 6 hours. The ethanol was removed in vacuo, and the residue was taken up in dichloromethane (150 ml). The suspension was extracted with water (3 x 50) and 0.5 N sodium hydroxide (2 x 50 ml). The aqueous extracts were combined, cooled in an ice bath, and the pH was adjusted to 3.5 with

concentrated hydrochloric acid. The orange, sticky precipitate was recrystallized from methanol/water to give 1.20 g (26%) of 1,2-dihydro-5-(3-sec-butoxy-benzyl)-2-thioxo-4(3H)-pyrimidinone, mp 127-130°C.

C. Preparation of 5-(3-sec-butoxybenzyl)uracil

A suspension of 1,2-dihydro-5-(3-sec-butoxybenzyl)-2-thioxo-4(3H)-pyrimidinone (0.60 g, 2.0 mmoles) in glacial acetic acid (10 ml) and 20% aqueous chloroacetic acid (10 ml) was refluxed with stirring for 18 hours. After cooling to ambient temperature and then in an ice bath, the mixture was filtered, and the solids were washed with water and diethyl ether and dried in a vacuum oven at 80°C for 18 hours to give 0.13 g (24%) of 5-(3-sec-butoxybenzyl)uracil as a white solid, mp 213-215°C.

D. Preparation of 1-((2-acetoxyethoxy)methyl)-5-(3-sec-butoxybenzyl)uracil

Bis(trimethylsilyl)acetamide (1.4 ml, 5.6 mmoles) was added to a stirred suspension of 5-(3-sec-butoxybenzyl)uracil (0.875 g, 3.2 mmoles) in dichloroethane (35 ml) under nitrogen. The mixture was refluxed with stirring for 35 minutes, the heat removed, and the solution which formed cooled in an ice bath. A solution of (2-acetoxyethoxy)methyl bromide (0.55 g, 2.8 mmoles) in acetonitrile (5 ml) was added to the cooled solution and the resulting solution allowed to warm to ambient temperature and stirred under nitrogen for 18 hours. The solvents were removed in vacuo and the residual oil introduced onto a column of Silica Gel 60 wetted with dichloromethane. The column was eluted with dichloromethane : methanol (99 : 1), and the fractions containing product were combined and evaporated in vacuo. The residue was dissolved in dichloromethane, washed with water (2 x 75 ml) and brine (75 ml), dried over anhydrous magnesium sulfate, filtered and evaporated in vacuo to give 0.80 g (64%) of 1-((2-acetoxy-ethoxy)methyl)-5-(3-sec-butoxy-benzyl)uracil as a clear oil; tlc, dichloromethane : methanol (19:1).

E. Preparation of 1-((2-hydroxyethoxy)methyl)-5-(3-sec-butoxybenzyl)uracil

A solution of 1-((2-acetoxyethoxy)methyl)-5-(3-sec-butoxybenzyl)uracil (0.80 g, 2.0 mmoles) in methanol (100 ml) saturated with ammonia gas was stirred in a stoppered flask for 18 hours at ambient temperature. The methanol was removed in vacuo, and the residue was crystallized from 2-propanol : hexane and dried in a vacuum oven at 48°C to give 0.48 g (67 %) of 1-((2-hydroxy-ethoxy)methyl)-5-(3-sec-butoxybenzyl)uracil as a white solid, mp 82-86°C; uv (0.1 N hydrochloric acid + 10% methanol): l 266 nm (e 10800); (pH 7 buffer + 10% methanol): l 266 nm (e 10800); (0.1 N sodium hydroxide + 10% methanol): l 266 nm (e 7500); NMR (DMSO-d_6): d 11.39 (s, 1H, NH), 7.67 (s, 1H, H-6), 6.96 (m, 4H, ArH), 5.10 (s, 2H, NCH_2O), 4.69 (s, 1H, OH), 4.33 (m, 1H, OCH), 3.50 (s, 6H, CH_2Ar and $(CH_2)_2$), 1.60 (m, 2H, $C\underline{H}_2CH_3$), 1.21 (d, 3H, $OCHC\underline{H}_3$), 0.85 (t, 3H, $CH_2C\underline{H}_3$); ms: m/e 349.
Anal. Calcd. for $C_{18}H_{24}N_2O_5$: C,62.05; H, 6.94; N, 8.04.
Found: C, 61.90; H, 6.93; N, 7.97.

Example 7

Preparation of 1-((2-hydroxyethoxy)methyl-5-(3-(3-fluorophenoxy)benzyl)uracil

A. Preparation of 3-bromo-3'-fluorodiphenyl ether

A solution of 3-fluorophenol (Aldrich) (8.25g, 74mmol) and 25% NaOMe in methanol (Aldrich) (18.5mL, 81mmol) was stirred for 3 hours at ambient temperature. The solution was concentrated in vacuo to a tan solid. The phenoxide was dissolved in N-methyl-2-pyrrolidinone (Aldrich) (50mL) and heated in a 180°C oil bath. 1-Bromo-3-fluorobenzene (Aldrich) (12.95g, 74mmol) was added and the mixture was stirred for 24 hours at 180°C. After cooling to room temperature, the reaction mixture was diluted with H_2O (100mL) and extracted with dichloromethane (2 x 100mL). The organic layer was concentrated to dryness in vacuo, redissolved in diethyl ether (100mL), washed with H_2O (100mL), saturated $NaHCO_3$ (100mL), dried over Na_2SO_4, filtered and concentrated in vacuo to a brown oil (12.5g). The oil was chromatographed on Silica Gel 60 using hexane. The fractions containing only

3-bromo-3'-fluorodiphenyl ether were combined and concentrated in vacuo to give 8.42g (43%) of a clear, colorless oil.

B. Preparation of ethyl 3-(3-(3-fluorophenoxy)phenyl)acrylate

A mixture of 3-bromo-3'-fluorodiphenyl ether (5.30g, 19.8mmol), ethyl acrylate (Aldrich) (2.48g, 24.8mmol), triethylamine (Kodak) (2.51g, 24.8mmol), palladium (II) acetate (Aldrich) (44.5mg, 0.2mmol), tri-o-tolylphosphine (Aldrich) (244mg, 0.8mmol), and acetonitrile (20mL) were added to a heavy-glass walled bottle, flushed with nitrogen, sealed and heated in a 100°C oil bath for 5 hours. Cold 0.1N HCl (40mL) was added to the cooled reaction mixture. The lower layer was collected and concentrated in vacuo to a dark-green oil and chromatographed on Silica Gel 60 with 0-3% ethyl acetate/hexanes as eluent. The fractions containing only ethyl 3-(3-(3-fluorophenoxy)phenyl)acrylate were combined and concentrated in vacuo to give 4.48g (79%) of a clear, colorless oil.

C. Preparation of ethyl 3-(3-(3-fluorophenoxy)phenyl)propionate

To a solution of ethyl 3-(3-(3-fluorophenoxy)phenyl)acrylate (6.33g, 22mmol) and absolute EtOH (100mL) was added platinum oxide hydrate (E.M. Science) (100mg, 0.44mmol). The mixture was shaken on a Parr apparatus under hydrogen atmosphere (30psi) for 6 hours. The mixture was filtered to remove the catalyst and concentrated in vacuo to give 5.91g (93%) of a clear, colorless oil.

D. Preparation of
1,2-dihydro-5-(3-(3-fluorophenoxy)benzyl)-2-thioxo-4(3H)-pyrimidinone

A solution of ethyl 3-(3-(3-fluorophenoxy)phenyl propionate (5.51 g, 19.0 mmoles) and ethyl formate (3.07 g, 41.4 mmoles) in diethyl ether (35 mL) was added dropwise with stirring to a solution of potassium tert-butoxide (1 M in THF, 47.0 mL, 47.0 mmoles) in diethyl ether (125 mL) cooled in an ice bath under nitrogen. The solution was stirred at ambient temperature for 18 hours, and the solvent was removed in vacuo. The residue was dissolved in 2-propanol

(50 mL), thiourea (2.89 g, 38.0 mmoles) was added, and the mixture was refluxed under nitrogen for 5 hours. The solvent was removed in vacuo, and the solid residue was washed with cold diethyl ether, dissolved in cold water, and the pH was adjusted to 4 with glacial acetic acid. The beige precipitate was collected on a filter, washed several times with water and diethyl ether, and dried under a vacuum at ambient temperature for 18 hours to give 3.29 g (53%) of 1,2-dihydro-5-(3-(3-fluorophenoxy)-benzyl)-2-thioxo-4(3H)-pyrimidinone, mp 170-172°C (dec.). Recrystallization of 0.40 g from methanol gave 0.20 g of an analytically pure sample.

E. Preparation of 5-(3-(3-fluorophenoxy)benzyl) uracil

A suspension of 1,2-dihydro-5-(3-(3-fluorophenoxy)benzyl)-2-thioxo-4(3H)-pyrimidinone (2.70 g, 8.2 mmoles) in glacial acetic acid (40 mL) and 20% aqueous chloroacetic acid (40 mL) was refluxed with stirring for 6 hours. After cooling to ambient temperature and then in an ice bath, the mixture was filtered, and the solids were washed with water and ether and dried in a vacuum oven at 80°C for 18 hours to give 2.34 g (91%) of 5-(3-(3-fluorophenoxy)benzyl) uracil as an off-white solid, mp 243-245°C. Recrystallization of 0.400 g from acetic acid-water gave 0.161 g of an analytically pure sample.

F. Preparation of 1-((2-acetoxyethoxy)methyl)-5-(3-(3-fluorophenoxy)-benzyl)uracil

Bis(trimethylsilyl)acetamide (1.38 mL, 5.6 mmoles) was added to a stirred suspension of 5-(3-(3-fluorophenoxy)benzyl)uracil (1.00 g, 3.2 mmoles) in dichloroethane (35 mL) under nitrogen. The mixture was refluxed with stirring for 1 hour, the heat was removed, and the solution which formed was cooled in an ice bath. A solution of (2-acetoxyethoxy)methyl bromide (0.55 g, 2.8 mmoles) in acetonitrile (4 mL) was added to the cooled solution, and the resulting solution allowed to warm to ambient temperature and stirred under nitrogen for 18 hours. The solvents were removed in vacuo, and the residue was dissolved in dichloromethane (75 mL) and washed with water (3 X 25 mL) and brine. The solvents were removed in vacuo, and the residual oil was introduced onto a column of Silica Gel 60 wetted with dichloromethane. The column was

eluted with dichloromethane : 2-propanol (100 : 2), and the fractions containing product were combined. The solvents were removed in vacuo to give 0.58 g (48%) of 1-((2-acetoxyethoxy)methyl)-5-(3- (3-fluorophenoxy)benzyl)uracil as a clear oil.

G. Preparation of 1-((2-hydroxyethoxy)methyl)-5-(3-(3-fluorophenoxy)-benzyl)uracil

A solution of 0.53 g (1.2 mmoles) of 1-((2-acetoxyethoxy)methyl)-5-(3-(3-fluorophenoxy)benzyl)uracil in methanol (75 mL) saturated with ammonia gas was stirred in a stoppered flask for 24 hours at ambient temperature. The methanol was removed in vacuo, and the residue was recrystallized from 2-propanol : hexane and dried in a vacuum oven at 80°C to give 0.282 g (74%) of 1-((2-hydroxyethoxy)methyl)-5-(3-(3-fluorophenoxy)benzyl)uracil as a white solid, mp 98-100°C; NMR (DMSO-d_6): d 11.40 (s, 1H, NH), 7.69 (s, 1H, H-6), 7.11 (m, 8H, ArH), 5.08 (s, 2H, NCH_2O), 4.68 (s, 1H, OH), 3.54 (s, 2H, CH_2Ar), 3.49 (s, 4H, $(CH_2)_2$); ms: m/e 387.
Anal. Calcd. for $C_{20}H_{19}FN_2O_5$: C, 62.17; H, 4.96; N, 7.25.
Found: C, 62.01; H, 5.00; N, 7.16.

Example 8

Preparation of
1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(3-fluorophenoxy)benzyl)uracil

A. Preparation of
2-((1,2,3,4-tetrahydro-2,4-dioxo-5-(3-(3-fluorophenoxy)benzyl)-1-pyrimidinyl)methoxy)-1,3-propanediyl dibenzoate 1/4 hydrate

Bis(trimethylsilyl)acetamide (1.30 mL, 5.3 mmoles) was added to a stirred suspension of 5-(3-(3-fluorophenoxy)benzyl)uracil (0.937 g, 3.0 mmoles) in dichloroethane (35 mL) under nitrogen. The mixture was refluxed with stirring for 35 minutes, and the resultant solution cooled in an ice bath. A solution of 2-(bromomethoxy)-1,3-propanediyl dibenzoate (0.76 g, 2.0 mmoles) in acetonitrile (4 mL) was added to the cooled solution, and the resultant solution

was allowed to warm to ambient temperature and stirred under nitrogen for 18 hours. The solvents were removed in vacuo, and the residue was dissolved in dichloromethane (75 mL) and washed with water (3 X 25 mL) and brine. The volatiles were removed in vacuo, and the residual oil was introduced onto a column of Silica Gel 60 wetted with dichloromethane. The column was eluted with dichloromethane : 2-propanol (50 : 1), the fractions containing product were combined, and the solvents were removed in vacuo to give 0.77 g (41%) of 2-((1,2,3,4-tetrahydro-2,4-dioxo-5-(3-(3-fluorophenoxy)benzyl)-1-pyrimidinyl)methoxy)-1,3-propanediyl dibenzoate _1/4 hydrate as a white solid, mp 158-161°C.

B. Preparation of 1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(3-fluoro-phenoxy)benzyl)uracil

A solution of 0.68 g (1.1 mmoles) of 2-((1,2,3,4-tetrahydro-2,4-dioxo-5-(3-(3-fluoro-phenoxy)benzyl)-1-pyrimidinyl)methoxy)-1,3-propanediyl dibenzoate in methanol (75 mL) saturated with ammonia gas was stirred in a stoppered flask for 24 hours at ambient temperature. The methanol was removed in vacuo, and the residue was dissolved in ethyl acetate and extracted with 0.3 N sodium hydroxide (4 x 25 mL). The combined aqueous extracts were cooled in an ice bath, neutralized with 1N hydrochloric acid, and extracted with ethyl acetate (3 x 50 mL). The ethyl acetate extracts were combined, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. Trituration of the residual oil with cold dichloromethane (20 mL) gave 0.161 (36%) of 1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(3-fluorophenoxy)benzyl) uracil as a white solid, mp 122-123°C. .

Example 9

Preparation of

1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(4-fluorophenoxy)benzyl)uracil

A. Preparation of 2-((1,2,3,4-tetrahydro-2,4-dioxo-5-(3-(4-fluorophenoxy)-benzyl)-1- pyrimidinyl)methoxy)-1,3-propanediyl dibenzoate

Bis(trimethylsilyl)acetamide (1.30 mL, 5.3 mmoles) was added to a stirred suspension of 5-(3-(4-fluorophenoxy)benzyl)uracil (0.937 g, 3.0 mmoles) in dichloroethane (35 mL) under nitrogen. The mixture was refluxed with stirring for 45 minutes, and the resultant solution cooled in an ice bath. A solution of 2-(bromomethoxy)-1,3-propanediyl dibenzoate (0.76 g, 2.0 mmoles) in acetonitrile (4 mL) was added to the cooled solution, and the resultant solution was allowed to warm to ambient temperature and stirred under nitrogen for 18 hours. The solvents were removed in vacuo, and the residue was dissolved in dichloromethane (75 mL) and washed with water (3 X 25 mL) and brine. The volatiles were removed in vacuo, and the residual oil introduced onto a column of Silica Gel 60 wetted with dichloromethane. The column was eluted with dichloromethane : 2-propanol (50 : 1), the fractions containing product were combined, and the solvents were removed in vacuo to give 0.853 g (45%) of 2-((1,2,3,4-tetrahydro-2,4-dioxo-5-(3-(4-fluorophenoxy)benzyl)-1-pyrimidinyl)methoxy)-1,3-propanediyl dibenzoate as a white solid, mp 155-158°C.

B. Preparation of 1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(4-fluoro-phenoxy)benzyl)uracil

A solution of 0.77 g (1.2 mmoles) of 2-((1,2,3,4-tetrahydro-2,4-dioxo-5-(3-(4-fluorophenoxy)benzyl)-1-pyrimidinyl)methoxy)-1,3-propanediyl dibenzoate in methanol (75 mL) saturated with ammonia gas was stirred in a stoppered flask for 24 hours at ambient temperature. The methanol was removed in vacuo, and the residue was dissolved in ethyl acetate and extracted with 0.1 N sodium hydroxide (6 x 15 mL). The combined aqueous extracts were allowed to stand at ambient temperature for 30 minutes and diluted with water. The precipitate

which formed was collected by filtration, washed with water, and dried in a vacuum oven at 100°C for 18 hours to give 0.168 g (33%) of 1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(4-fluorophenoxy)benzyl) uracil as a white solid, mp 147-148°C; NMR (DMSO-d_6): s 11.35 (s, 1H, NH), 7.65 (s, 1H, H-6), 7.03 (m, 8H, ArH), 5.17 (s, 2H, NCH_2O), 4.63 (t, 2H, OH), 3.58 (s, 2H, CH_2Ar), 3.36 (m, 5H, CH and 2($C\underline{H}_2OH$)); ms: m/e 417.
Anal. Calcd. for $C_{21}H_{21}FN_2O_6$: C, 60.57; H, 5.08; N, 6.73.
Found: C, 60.46; H, 5.11; N, 6.64.

Example 10

Preparation of 1-((2-hydroxyethoxy)methyl)-5-(3-(2-fluorophenoxy)benzyl) uracil

A. Preparation of ethyl 3-(3-(2-fluorophenoxy)phenyl)propionate

This compound was prepared from 2-fluorophenol (Aldrich) in an analogous manner to that of Examples 7A to 7C with the replacement of ethyl 3-(3-(3-fluorophenoxy)phenyl)acrylate with ethyl 3-(3-(2-fluorophenoxy) phenyl) acrylate (3.20g, 11.2mmol). The filtrate was concentrated in vacuo and chromatographed on Silica Gel 60 using 5% EtOAc/hexanes. The fractions containing only ethyl 3-(3-(2-fluorophenoxy) phenyl)propionate were combined and concentrated to give 1.16g (36%) of a clear, colorless oil.

B. Preparation of 1,2-dihydro-5-(3-(2-fluorophenoxy)benzyl)-2-thioxo-4(3H)-pyrimidinone

A solution of ethyl 3-(3-(2-fluorophenoxy)phenyl propionate (11.95 g, 41.4 mmoles) and ethyl formate (6.62 g, 89.3 mmoles) in diethyl ether (80 ml) was added dropwise with stirring to a solution of potassium tert- butoxide (1 M in THF, 102.0 ml, 102.0 mmoles) in diethyl ether (200 ml) cooled in an ice bath under nitrogen. The solution was stirred at ambient temperature for 18 hours, and the solvent was removed in vacuo. The residue was dissolved in 2-propanol (100 ml), thiourea (6.30 g, 82.8 mmoles) was added, and the mixture was refluxed under nitrogen for 5 hours. The solvent was removed in vacuo, and the solid residue was washed with cold diethyl ether, dissolved in cold water, and the pH was adjusted to 4 with glacial acetic acid. The beige precipitate was collected

on a filter, washed several times with water and diethyl ether, and dried under a vacuum at 70°C for 18 hours to give 7.92 g (58%) of 1,2-dihydro-5-(3-(2-fluorophenoxy)benzyl)-2-thioxo-4(3H)-pyrimidinone, mp 210-213°C (dec.). Recrystallization of 0.40 g from methanol gave 0.28 g of an analytically pure sample.

C. Preparation of 5-(3-(2-fluorophenoxy)benzyl) uracil

A suspension of 1,2-dihydro-5-(3-(2-fluorophenoxy)benzyl)-2-thioxo-4(3H)-pyrimidinone (7.515 g, 22.9 mmoles) in glacial acetic acid (110 ml) and 20% aqueous chloroacetic acid (110 ml) was refluxed with stirring for 5 hours. After cooling to ambient temperature and then in an ice bath, the mixture was filtered, and the solids were washed with water and ether and dried in a vacuum oven at 80°C for 18 hours to give 6.45 g (90%) of 5-(3-(2-fluorophenoxy)benzyl) uracil as an off-white solid, mp = 266-268°C.

D. Preparation of 1-((2-acetoxyethoxy)methyl)-5-(3-(2-fluorophenoxy)benzyl) uracil

Bis(trimethylsilyl)acetamide (2.8 ml, 11.4 mmoles) was added to a stirred suspension of 5-(3-(2-fluorophenoxy)benzyl) uracil (2.0 g, 6.4 mmoles) in dichloroethane (65 ml) under nitrogen. The mixture was refluxed with stirring for 1.5 hours, the heat removed, and the solution which formed cooled in an ice bath. A solution of (2-acetoxyethoxy)methyl bromide (1.2 g, 6.1 mmoles) in acetonitrile (8 ml) was added to the cooled solution and the resulting solution allowed to warm to ambient temperature and stirred under nitrogen for 18 hours. The solvents were removed in vacuo, and the residue was dissolved in dichloromethane (50 ml) and washed with water (3 X 25 ml) and brine. The solvents were removed in vacuo and the residual oil introduced onto a column of Silica Gel 60 wetted with dichloromethane. The column was eluted with dichloromethane : 2-propanol (100 : 1), and the fractions containing product were combined and evaporated in vacuo to give 2.16 g (83%) of 1-((2-acetoxyethoxy)methyl)-5-(3-(2-fluorophenoxy)benzyl) uracil as a sticky yellow

oil, which was used without further purification; tlc, dichloromethane : methanol- (19:1).

E. Preparation of 1-((2-hydroxyethoxy)methyl)-5-(3-(2-fluorophenoxy)benzyl) uracil

A solution of 2.13 g (5.0 mmoles) of 1-((2-acetoxyethoxy)methyl)-5-(3-(2-fluorophenoxy)benzyl) uracil in methanol (60 ml) saturated with ammonia gas was stirred in a stoppered flask for 24 hours at ambient temperature. The methanol was removed in vacuo, and the residue was recrystallized from 2-propanol and dried in a vacuum oven at 70°C to give 0.96 g (50 %) of 1-((2-hydroxyethoxy)methyl)-5-(3-(2-fluorophenoxy)benzyl)uracil as a white solid, mp 107-108°C; NMR (DMSO-d_6): d 11.40 (s, 1H, NH), 7.68 (s, 1H, H-6), 7.07 (m, 8H, ArH), 5.08 (s, 2H, NCH_2O), 4.67 (m, 1H, OH), 3.52 (s, 2H, CH_2Ar), 3.48 (s, 4H, $(CH_2)_2$) ; ms: m/e 387.
Anal. Calcd. for $C_{20}H_{19}FN_2O_5$: C, 62.17; H, 4.96; N, 7.25.
Found: C, 62.29; H, 5.01; N, 7.26.

Example 11

Preparation of 1-((2-hydroxyethoxy)methyl)-5-(3-(3-chlorophenoxy)benzyl) uracil

A. Preparation of ethyl 3-(3-(3-chlorophenoxy)phenyl)acrylate

This compound was prepared in an analogous manner to that of Example 7A and 7B with the replacement of 3-fluorophenol with 3-chlorophenol (Aldrich) (10.0g, 77.8mmd). The chromatography fractions that contained only ethyl 3-(3-(3-chlorophenoxy)phenyl)acrylate were combined and concentrated in vacuo to give 14.40g (79%) of a clear, colorless oil.

B. Preparation of ethyl 3-(3-(3-chlorophenoxy)phenyl)propionate

To a solution of ethyl 3-(3-(3-chlorophenoxy)phenyl)acrylate (14.4g, 48mmol) and absolute EtOH (100mL) was added platinum oxide hydrate (E.M. Science) (0.50g, 2.2mmol). The mixture was stirred under hydrogen atmosphere at ambient pressure until hydrogen uptake stopped (approx. 1.1l). The mixture

was filtered to remove the catalyst and concentrated in vacuo. The oil was chromatographed on Silica Gel 60 with 10% EtOAc/hexanes. The fractions containing only ethyl 3-(3-(3-chlorophenoxy)phenyl)propionate were combined and concentrated in vacuo to give 12.7g (87%) of a clear, colorless oil.

C. Preparation of 1,2-dihydro-5-(3-(3-chlorophenoxy)benzyl)-2-thioxo-4(3H)-pyrimidinone

A solution of ethyl 3-(3-(3-chlorophenoxy)phenyl propionate (12.40 g, 40.7 mmoles) and ethyl formate (6.60 g, 88.8 mmoles) in diethyl ether (90 ml) was added dropwise with stirring to a solution of potassium tert-butoxide (1 M in THF, 102.0 ml, 102.0 mmoles) in diethyl ether (210 ml) cooled in an ice bath under nitrogen. The solution was stirred at ambient temperature for 18 hours, and the solvent was removed in vacuo. The residue was dissolved in 2-propanol (100 ml), thiourea (6.20 g, 81.4 mmoles) was added, and the mixture was refluxed under nitrogen for 5 hours. The solvent was removed in vacuo, and the solid residue was washed with cold diethyl ether, dissolved in cold water, and the pH was adjusted to 4 with glacial acetic acid. The beige precipitate was collected on a filter, washed several times with water and diethyl ether, and dried under a vacuum at 70°C for 18 hours to give 7.64 g (54%) of 1,2-dihydro-5-(3-(3-chlorophenoxy)benzyl)-2-thioxo-4(3H)-pyrimidinone, mp 163-165°C (dec.). Recrystallization of 0.39 g from methanol gave 0.265 g of an analytically pure sample.

D. Preparation of 5-(3-(3-chlorophenoxy)benzyl) uracil

A suspension of 1,2-dihydro-5-(3-(3-chlorophenoxy)benzyl)-2-thioxo-4(3H)-pyrimidinone (6.40 g, 18.6 mmoles) in glacial acetic acid (90 ml) and 20% aqueous chloroacetic acid (90 ml) was refluxed with stirring for 18 hours. After cooling to ambient temperature and then in an ice bath, the mixture was filtered, and the solids were washed with water and ether and dried in a vacuum oven at 80°C for 18 hours to give 5.39 g (88%) of 5-(3-(3-chlorophenoxy)benzyl) uracil as an off-white solid, mp 209-211°C.

E. Preparation of 1-((2-acetoxyethoxy)methyl)-5-(3-(3-chlorophenoxy)benzyl) uracil

Bis(trimethylsilyl)acetamide (2.6 ml, 10.6 mmoles) was added to a stirred suspension of 5-(3-(3-chlorophenoxy)benzyl) uracil (2.0 g, 6.0 mmoles) in dichloroethane (65 ml) under nitrogen. The mixture was refluxed with stirring for 1.5 hours, the heat removed, and the solution which formed cooled in an ice bath. A solution of (2-acetoxyethoxy)methyl bromide (0.95 g, 4.8 mmoles) in acetonitrile (8 ml) was added to the cooled solution and the resulting solution allowed to warm to ambient temperature and stirred under nitrogen for 18 hours. The solvents were removed in vacuo, and the residue was dissolved in dichloromethane (100 ml) and washed with water (3 X 25 ml) and brine. The solvents were removed in vacuo and the residual oil introduced onto a column of Silica Gel 60 wetted with dichloromethane. The column was eluted with dichloromethane : 2-propanol (100 : 1), and the fractions containing product were combined and evaporated in vacuo to give 1.61 g (74%) of 1-((2-acetoxyethoxy)methyl)-5-(3-(3-chlorophenoxy)benzyl) uracil as a clear oil, which was used without further purification; tlc, dichloromethane : methanol (19 :1).

F. Preparation of 1-((2-hydroxyethoxy)methyl)-5-(3-(3-chlorophenoxy)benzyl) uracil

A solution of 1.60 g (3.6 mmoles) of 1-((2-acetoxyethoxy)methyl)-5-(3-(3-chlorophenoxy)benzyl) uracil in methanol (150 ml) saturated with ammonia gas was stirred in a stoppered flask for 24 hours at ambient temperature. The methanol was removed in vacuo, and the residue was recrystallized from 2-propanol : hexane and dried in a vacuum oven at 70°C to give 1.27 g (88%) of 1-((2-hydroxyethoxy)methyl)-5-(3-(3-chlorophenoxy)benzyl) uracil as a white solid, mp = 118-120°C; NMR (DMSO-d_6): d 11.30 (s,1H, NH), 7.71 (s, 1H, H-6), 7.16 (m, 8H, ArH), 5.10 (s, 2H, NCH_2O), 4.71 (m, 1H, OH), 3.56 (s, 2H, CH_2Ar), 3.50 (s, 4H, $(CH_2)_2$); ms: m/e 403 (M+).
Anal. Calcd. for $C_{20}H_{19}ClN_2O_5$: C, 59.63; H, 4.75; N, 6.96.
Found: C, 59.661; H, 4.77; N, 6.91.

Example 12

Preparation of 1-((2-hydroxyethoxy)methyl)-5-(3-(3-cyanophenoxy)benzyl)uracil

A. Preparation of 3-bromo-3'-cyanodiphenyl ether

3-Cyanophenol (Aldrich) (19.06 g, 160 mmoles) was added to a solution of sodium (3.90 g, 170 mmoles) in methanol (140 ml). The solution was stirred for 18 hours at ambient temperature, and the methanol was removed in vacuo . The phenoxide was dissolved in N-methyl-2-pyrrolidinone (Aldrich) (100 ml) and heated in a 175°C oil bath. 1-Bromo-3-fluorobenzene (Aldrich) (28.0 g, 160 mmoles) was added, and the solution was stirred for 3 days at 170-180°C. After cooling to ambient temperature, the mixture was diluted with water (400 ml) and extracted with dichloromethane (3 x 150 ml). The combined extracts were concentrated in vacuo, and the residue was dissolved in diethyl ether (300 ml). The ether solution was washed with water (3 x 150 ml) and brine (150 ml) and concentrated in vacuo. The residue was chromatographed on Silica Gel 60 eluting with hexane. The fractions containing product were combined and evaporated in vacuo to give 20.10 g (46%) of crude 3-bromo-3'-cyanodiphenyl ether as a clear oil which was used without further purification.

B. Preparation of (E)-ethyl 3-(3-(3-cyanophenoxy)phenyl)acrylate

This compound was prepared in an analogous manner to that of Example 14B with the replacement of 3-bromo-3'-fluorodiphenyl ether with 3-bromo-3'-cyanodiphenyl ether (19.0 g, 69.3 mmoles). The chromatography fractions containing product were combined and evaporated in vacuo to give 18.38 g (90%) of (E)-ethyl 3-(3-(3-cyanophenoxy)phenyl)acrylate as a yellow oil.

C. Preparation of ethyl 3-(3-(3-cyanophenoxy)phenyl)propionate

A mixture of (E)-ethyl 3-(3-(3-cyanophenoxy)phenyl)acrylate (0.75 g, 2.6 mmoles), 10% palladium-carbon (0.200 g) and 95% ethanol (170 ml) was shaken in the presence of hydrogen at 2-3 atmospheres for four hours. The catalyst was removed by filtration through Celite, and the ethanol was removed

from the filtrate in vacuo. The residue was chromatographed on Silica Gel 60, eluting with hexane : ethyl acetate (9 : 1), and the fractions containing product with Rf=0.5 in hexane : ethyl acetate (19 : 1) were combined and evaporated in vacuo to give 0.54 g (70%) of ethyl 3-(3-(3-cyanophenoxy)phenyl)propionate as a clear oil.

D. Preparation of 1,2-dihydro-5-(3-(3-cyanophenoxy)benzyl)-2-thioxo-4(3H)-pyrimidinone

A solution of ethyl 3-(3-(3-cyanophenoxy)phenyl propionate (7.52 g, 25.5 mmoles) and ethyl formate (4.17 g, 56.3 mmoles) in diethyl ether (50 ml) was added dropwise with stirring to a solution of potassium tert- butoxide (1 M in THF, 64.0 ml, 64.0 mmoles) in diethyl ether (165 ml) cooled in an ice bath under nitrogen. The solution was stirred at ambient temperature for 18 hours, and the solvent was removed in vacuo. The residue was dissolved in 2-propanol (65 ml), thiourea (3.92 g, 51.5 mmoles) was added, and the mixture was refluxed under nitrogen for 5 hours. The solvent was removed in vacuo, and the solid residue was washed with cold diethyl ether, dissolved in cold water, and the pH was adjusted to 4 with glacial acetic acid. The yellow sticky solid was washed several times with water and diethyl ether to give 7.20 g (84%) of crude 1,2-dihydro-5-(3-(3-cyanophenoxy)benzyl)-2-thioxo-4(3H)-pyrimidinone which was used without further purification. Recrystallization of 1.00 g from methanol followed by trituration with acetonitrile gave 0.14 g of 1,2-dihydro-5-(3-(3-cyanophenoxy)benzyl)-2-thioxo-4(3H)-pyrimidinone; mp 203-205°C.

E. Preparation of 5-(3-(3-cyanophenoxy)benzyl) uracil

A suspension of 1,2-dihydro-5-(3-(3-cyanophenoxy)benzyl)-2-thioxo-4(3H)-pyrimidinone (6.00 g, 17.9 mmoles) in glacial acetic acid (100 ml) and 20% aqueous chloroacetic acid (100 ml) was refluxed with stirring for 18 hours. After cooling to ambient temperature and then in an ice bath, the mixture was filtered, and the solids were washed with water and ether and dried in a vacuum oven at 80°C for 3 days to give 3.05 g (53%) of 5-(3-(3-cyanophenoxy)benzyl)

uracil as a beige solid which was used without further purification, mp 179-185°C.

F. Preparation of 1-((2-acetoxyethoxy)methyl)-5-(3-(3 cyanophenoxy)benzyl)uracil

Bis(trimethylsilyl)acetamide (2.80 ml, 11.3 mmoles) was added to a stirred suspension of 5-(3-(3-cyanophenoxy)benzyl)uracil (2.00 g, 5.5 mmoles) in dichloroethane (65 ml) under nitrogen. The mixture was refluxed with stirring for 1 hour, the heat was removed, and the solution which formed was cooled in an ice bath. A solution of (2-acetoxyethoxy)methyl bromide (0.84 g, 4.2 mmoles) in acetonitrile (7 ml) was added to the cooled solution, and the resulting solution was allowed to warm to ambient temperature and stirred under nitrogen for 18 hours. The solvents were removed in vacuo, and the residue was dissolved in dichloromethane (150 ml) and washed with water (3 X 50 ml) and brine. The solvents were removed in vacuo, and the residual oil was introduced onto a column of Silica Gel 60 wetted with dichloromethane. The column was eluted with dichloromethane : 2-propanol (100 : 2), and the fractions containing product were combined. The solvents were removed in vacuo to give 1.76 g (64%) of 1-((2-acetoxyethoxy)methyl)-5-(3-(3-cyanophenoxy)benzyl)uracil as a clear oil which was used without further purification.

G. Preparation of 1-((2-hydroxyethoxy)methyl)-5-(3-(3 cyanophenoxy)benzyl)uracil

A solution of 1.74 g (4 mmoles) of 1-((2-acetoxyethoxy)methoxy)-5-(3-(3-cyanophenoxy)benzyl)uracil in methanol (150 ml) saturated with ammonia gas was stirred in a stoppered flask for 24 hours at ambient temperature. The methanol was removed in vacuo, and the residue was recrystallized from 2-propanol and dried in a vacuum oven at 80°C to give 0.97 g (62 %) of 1-((2-hydroxyethoxy)methyl)-5-(3-(3-cyanophenoxy)benzyl)uracil as a white solid, mp 115-117°C.

Example 13

Preparation of 1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(3-chlorophenoxy)benzyl)-uracil

A. Preparation of 2-((1,2,3,4-tetrahydro-2,4-dioxo-5-(3-(3-chlorophenoxy)benzyl)-1-pyrimidinyl)methoxy)-1,3-propanediyl dibenzoate

This compound was prepared in an analogous manner to that of Example 12F with the replacement of 0.95 g of (2-acetoxyethoxy)methyl bromide in Example 19F with 1.89 g of 2-(bromomethoxy)-1,3-propanediyl dibenzoate. The chromatography fractions were spin evaporated in vacuo to give 2.42 g of a clear oil. Trituration with acetonitrile gave 1.94 g (50%) of 2-((1,2,3,4-tetrahydro-2,4-dioxo-5-(3-(3-chlorophenoxy)benzyl)-1-pyrimidinyl)methoxy)-1,3-propanediyl dibenzoate as a white solid; mp 147-148°C.

B. Preparation of 1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(3-chlorophenoxy)-benzyl)uracil

This compound was prepared in an analogous manner to that of Example 12G with the replacement of 1.60 g of 1-((2-acetoxyethoxy)methyl)-5-(3-(3-chlorophenoxy)benzyl)uracil in Example 19G with 1.82 g of 2-((1,2,3,4-tetrahydro-2,4-dioxo-5-(3-(3-chlorophenoxy)benzyl)-1-pyrimidinyl)methoxy)-1,3-propanediyl dibenzoate. The methanol was removed in vacuo, and the residue was dissolved in ethyl acetate (100 ml) and extracted with 0.3 N NaOH (5 x 50 ml). The aqueous extracts were cooled in an ice bath, neutralized with 1 N hydrochloric acid, and extracted with ethyl acetate (3 x 100 ml). The organic extracts were washed with brine, dried over sodium sulfate, filtered, and evaporated in vacuo. The residue was recrystallized from dichloromethane and dried in a vacuum for 3 days to give 0.366 g (30 %) of 1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(3-chlorophenoxy)benzyl)uracil as a white solid, mp 118-119°C; uv (0.1 N hydrochloric acid + 10% methanol): l max 266 nm (Î 11600); (pH 7 buffer + 10% methanol): l max 267 nm (Î 10100); (0.1 N sodium hydroxide + 10% methanol): l max 266 nm (Î 8300); nmr (DMSO-d_6): d 11.35 (s, 1H, NH),

7.67 (s, 1H, H-6), 7 11 (m, 8H, ArH), 5.17 (s, 2H, NCH_2O), 4.62 (t, 2H, OH), 3.58 (s, 2H, CH_2Ar), 3.42 (m, 5H, CH and CH_2OH) ; ms: m/e 433 (M+).
Anal. Calcd. for $C_{21}H_{21}ClN_2O_6$: C, 58.27; H, 4.89; N, 6.47; Cl, 8.19.
Found: C, 58.19; H, 4.85; N, 6.44; Cl, 8.29.

Example 14

A. Preparation of 5-(3-chlorobenzyl)-1-(4-hydroxybutyl)uracil

A suspension of 5-(3-chlorobenzyl)uracil (3.00 g, 12.7 mmoles), bromobutyl acetate (0.61 ml, 4.2 mmoles) and cesium carbonate (4.14 g, 12.7 mmoles) was heated with stirring at 80-90°C for 1.5 hours. After cooling to ambient temperature, the cesium carbonate was removed by filtration and washed with dichloromethane. The filtrate and washings were combined and evaporated in vacuo to give a beige solid. Chromatography on Silica Gel 60, eluting with dichloromethane:methanol (33:1), gave 0.56 g of a clear oil which was shown by tlc analysis to be a mixture of three products. The oil was refluxed in a solution of sodium methoxide (0.086 g, 1.6 mmoles) and methanol (10 ml) for 1.5 hours under nitrogen. After cooling to ambient temperature, the methanol was removed in vacuo and the residue chromatographed on Silica Gel 60 eluting with dichloromethane:methanol (33:1). One pure fraction was obtained which, after evaporation in vacuo, gave 0.110 g of 5-(3-chlorobenzyl-1-(4-hydroxybutyl)uracil as a white solid, mp 125-127°C; tlc, dichloromethane:methanol (33:1), uv (0.1 N hydrochloric acid + 10% methanol): l_{max} 274 nm (e 10400); (pH 7 buffer + 10% methanol): l_{max} 274 nm (e 9800); (0.1 N sodium hydroxide + 10% methanol): l_{max} 272 nm (e 7100); NMR (DMSO-d_6): d 7.18 (m, 4H, Ar), 6.88 (s, 1H, H-6), 3.71 (m, 4H, NCH_2 and CH_2O), 3.62 (s, 2H, CH_2Ar), 1.68 (m, 5H, CCH_2CH_2C and OH);
ms: m/e 309 (M+).
Anal. Calcd. for $C_{15}H_{17}N_2O_3Cl$: C, 58.35; H, 5.55; N, 9.07.
Found: C, 58.31; H, 5.60; N, 9.06.

The following compounds of formula (I) were also made by methods analogous to, or adapted from that described in Example 1.

Example No.

15 5-(3-chlorobenzyl)-1-((2-hydroxyethoxy) methyl)uracil from 1-((2-acetoxyethoxy)methyl)-5-(3-chlorobenzyl)uracil.

mpt: 157 - 159°C

16 1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-chlorobenzyl)uracil from 2-((5-(3-chlorobenzyl)-1,2,3,4-tetrahydro-2,4-dioxo-1-pyrimidinyl)-methoxy)-1,3-propanediyl dipivalate.

Colourless Oil.
NMR (DMSO - d_6): d 11.33 (s, 1H, NH), 7.71 (s, 1H, H-6), 7.25 (m, 4H, ArH), 5.16 (s, 2H, NCH_2 O), 4.61 (t, 2H, OH), 3.52 (s, 2H, CH_2 Ar), 3.42 (m, 5H, CH and $C\underline{H}_2OH$).

17 1-((2-hydroxyethoxy)methyl)-5-(3-allyloxybenzyl)uracil from 1-((2-acetoxyethoxy)methyl)-5-(3-allyloxybenzyl)uracil.

mpt: 89 - 93°C

18 1-((3-hydroxypropoxy)methyl)-5-(3-propoxybenzyl)uracil from 1-((3-acetoxypropoxy)methyl)-5-(3-propoxybenzyl)uracil.

Clear Oil.
NMR (DMSO-d_6): d 8.25 (s,1H, NH), 7.30(s, 1H, H-6), 7.10 (m, 4H, ArH), 5.08 (s, 2H, NCH_2O), 3.91 (t, 2H, $ArOC\underline{H}_2$), 3.66 (m, 5H, $C\underline{H}_2$ Ar and OH and NCH_2OCH_2), 1.78 (m, 4H, $2(OC\underline{H}_2CH_2)$), 1.04(t,3H,CH_3).

19 1-((2-hydroxyethoxy)methyl)-5-(3,5-difluorobenzyl)uracil from 1-((2-acetoxy ethoxy)methyl-5-(3,5-difluorobenzyl)uracil.

mpt: 138 - 139°C

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20 1-((2-hydroxyethoxy)methyl)-5-(3-trifluoromethoxy)benzyl)uracil from 1-((2-acetoxyethoxy)methyl)-5-(3-trifluoromethoxy)benzyl)uracil.

mpt: 92 - 93°C

21 1-((2-hydroxyethoxy)methyl)-5-(3-(4-fluorophenoxy)benzyl)uracil from 1-((2-acetoxyethoxy)methyl)-5-(3-(4-fluorophenoxy)benzyl)uracil.

mpt: 106 - 109°C

22 1-((2-hydroxyethoxy)methyl)-5-(3-(3-methoxyphenoxy)benzyl)uracil from 1-((2-acetoxyethoxy)methyl)-5-(3-(3-methoxyphenoxy)benzyl) uracil.

mpt: 98 - 102°C

23 1-((2-hydroxyethoxy)methyl)-5-(3-(3-trifluoromethylphenoxy)benzyl) uracil from 1-((2-acetoxy ethoxy)methyl)-5-(3-(3-trifluoromethyl phenoxy)benzyl)uracil.

mpt: 103 - 105°C

24 1-((2-hydroxyethoxy)methyl)-5-(3-(3-methylphenoxy)benzyl)uracil from 1-((2-acetoxyethoxy)methyl)-5-(3-(3-methylphenoxy)benzyl)uracil.

mpt: 110 -111°C

25 1-((2-hydroxyethoxy)methyl)-5-(3-isobutoxybenxyl)uracil from 1-((2-acetoxyethoxy)methyl)-5-(3-isobutoxybenzyl)uracil.

mpt: 95 - 97°C

26 1-((2-hydroxyethoxy)methyl)-5-(3-butoxybenzyl)uracil from 1-((2-acetoxyethoxy)methyl)-5-(3-butoxybenzyl)uracil.

NMR (DMSO - d_6): d 11.25 (s, 1H, NH), 7.63 (s, 1H, H-6), 6.95 (m, 4H, ArH), 5.08 (s, 2H, NCH_2O), 4.67 (t, 1H, OH), 3.91 (t, 2H, $ArOCH_2$), 3.49 (m, 6H, CH_2Ar and $(CH_2)_2$), 1.67 (m, 2H, Ar $OCH_2C\underline{H}_2$), 1.43 (m, 2H, $C\underline{H}_2$ CH_3), 0.92 (t, 3H, CH_3).

27 1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl-5-(3-(3-fluoropropoxy)benzyl)uracil from 2-((1,2,3,4 - tetrahydro-2, 4 - dioxo-5-(3-(3-fluoropropoxy)benzyl)-1-pyrimidinyl)methoxy)-1,3-propanediyl dibenzoate.

mpt: 99 - 101°C

Example 28

In-vitro Inhibition of Uridine Phosphorylase

Method

Preparation of enzyme-- Fresh livers, obtained from female CD-1 mice under Fluothane or carbon dioxide anesthesia, were weighed then homogenized in ice cold (3:1, v/w) 20 mM potassium phosphate buffer pH 8, 1mM EDTA, 1 mM mercaptoethanol. The homogenate was centrifuged at 100000 x g for 1 hour at 4°C, and the supernatant was used as the enzyme source.

Enzyme inhibition studies-- Assays were conducted in 20 mM potassium phosphate buffer, pH 8, 1 mM EDTA, 1 mM dithiothreitol containing 170 mM [2-^{14}C] uridine (7 mCi/mmole), various amounts of inhibitor or buffer and 20 mL of enzyme in a final volume of 60 mL. The reaction was carried out for 30 minutes 37°C then terminated by boiling for 1 minute. Precipated proteins were removed by centrifugation, and 5mL of the supernatant were spotted on silica gel thin layer chromatography sheets (with fluorescence indicator) that were prespotted with 5 mL of a mixture of 10 mM each uracil and uridine. The plates were developed in chloroform:methanol:acetic acid (90:5:5), and uridine and uracil were detected by UV quenching. The pyrimidines areas were cut out and counted by liquid scintillation in 5ml of Ready Safe (Beckman). The cpm (velocity) of the inhibitor containing samples were compared to those of the control, and percent inhibition values were calculated. Plots of percentage of inhibition versus the logarithm of inhibitor concentration were used to

calculate the IC_{50} values (the concentration of inhibitor needed to give a 50% reduction of the enzyme reaction rate) shown below.

Compound of example:	IC50 mM
1	<0.05
2	0.06
3	<0.05
4	<0.05
5	0.068
6	<0.05
7	<0.05
8	<0.05
9	<0.05
10	0.063
11	<0.05
12	<0.05
13	<0.05
14	0.43
15	0.3
16	0.11

The following Examples illustrate pharmaceutical formulations in which the "Active Ingredient" is a compound of formula I, preferably:

1-((2-hydroxy-1-(hydroxymethyl) thoxy)methyl)-(3-phenoxybenzyl)uracil,
1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(3-fluorophenoxy)benzyl)uracil,
1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(4-fluorophenoxy)benzyl)uracil
1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-5-(3-(3-chlorophenoxy)benzyl)uracil
or
1-((2-hydroxyethoxy)methyl)-5-(3-(3-cyanophenoxy)benzyl)uracil.

Example 29
Tablet Formulations

The following formulations 29A, 29B and 29C are prepared by wet granulation of the ingredients (except the magnesium stearate) with a solution of the povidone followed by drying of the granules, addition of the magnesium stearate and compression.

Formulation 29A	mg/tablet	mg/tablet
Active ingredient	100	10
Lactose, B.P.	200	60
Povidone, B.P.	20	10
Sodium starch glycollate	20	10
Magnesium stearate	10	10
	350	100

Formulation 29B	mg/tablet	mg/tablet
Active ingredient	100	10
Lactose, B.P.	150	60
Avicel PH 101	50	25
Povidone, B.P.	15	10
Sodium starch glycollate	20	10
Magnesium stearate	15	5
	350	120

Formulation 29C	mg/tablet
Active ingredient	100
Lactose, B.P.	200
Starch	40
Povidone, B.P.	6
Magnesium stearate	4
	350

The following formulation 29D is prepared by direct compression of the admixed ingredients. The lactose used is of the direct compression type.

Formulation 29D	mg/tablet
Active ingredient	100
Lactose	150
Avicel PH 101	100
	350

The following formulation 29E is a controlled release tablet and is prepared by wet granulation of the ingredients (except magnesium stearate) with a solution of the povidone, followed by drying of the granules, addition of the magnesium stearate and compression.

Formulation 29E	mg/tablet
Active ingredient	100
Hydroxypropylmethylcellulose (Methocel K4M Premium)	100
Lactose, B.P.	50
Povidone, B.P.	30
Magnesium stearate	20
	300

Example 30

Capsule Formulations

The following formulations 30A and 30B are prepared by admixing the uncompressed ingredients and filling into a two-part hard gelatin capsule.

Formulation 30A	mg/capsule
Active ingredient	10
Lactose, B.P.	250
Sodium starch glycollate	25
Magnesium stearate	5
	290

Formulation 30B	mg/capsule
Active ingredient	100
Pregelatinized starch NF15	250
	350

Formulation 30C	mg/capsule
Active ingredient	10
Macrogol 4000, B.P.	340
	350

The Macrogol 4000, B.P. is melted and the active ingredient dispersed therein. The thoroughly mixed melt is then filled into a two-part hard gelatin capsule.

Example 31

Injectable Formulation

Active ingredient	100mg
Sterile, pyrogen free phosphate buffer (pH 7.0), q.s. to	10ml

The active ingredient is dissolved in most of the phosphate buffer (35-40°C), then made up to volume and filtered through a sterile micropore filter into a 10 ml amber glass vial (type 1) and sealed with a sterile closure and overseal.

Example 32

Suppository Formulation

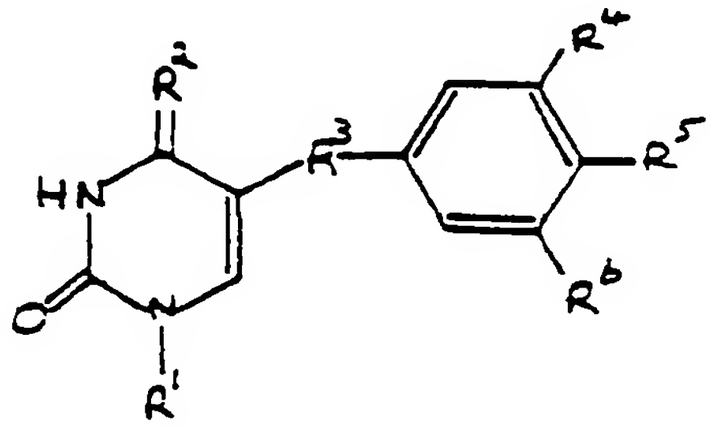
	mg/suppository
Active ingredient, 63 m*	100
Hard fat, B.P. (Witepsol H15-Dynamit Nobel)	1700
	1800

*The active ingredient is used as a powder wherein at least 90% of the particles are of 63 m or less. The symbol "m" as used herein means micron.

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200 m sieve and added to the molten base with mixing, using a silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension and stirred to ensure a homogeneous mix. The entire suspension is passed through a 250 m stainless steel screen and, with continuous stirring, is allowed to cool to about 40°C. At a temperature of 38°C to 40°C, 1.80 g of the mixture is filled into suitable plastic moulds. The suppositories are allowed to cool to room temperature.

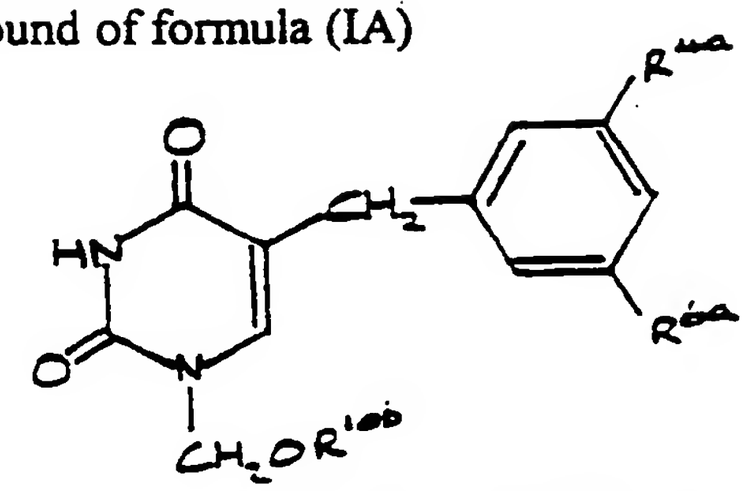
CLAIMS

1) A compound of formula (I)

(I) 

and esters and prodrugs thereof wherein R^1 is H, C_{1-8} straight or branched-chain alkyl, C_{2-6} alkenyl, or (C_{1-3} alkyl-C_{3-6} cycloalkyl-C_{1-3} alkyl) optionally substituted by 1 or 2 substituents selected from -OR^8 or-NR^8R^9(wherein $R^8$and R^9 are the same or different and are selected from H, C_{1-6} straight or branched-chain alkyl, and aralkyl); or a -CH_2ZR^{10}, -ZCH_2R^{10}, or $CH_2ZR^{10a}ZR^{10}$ group(wherein R^{10a} is selected from C_{1-6} straight or branched-chain alkylene and R^{10} is selected from C_{1-6} straight or branched chain alkyl) each of R^{10a} and R^{10} being optionally substituted by 1 or 2 substituents independently selected from -OR^8 and-NR^8R^9(wherein R^8 and R^9 are as defined above) and Z is selected from O, S, -CH_2O-, or -CH_2S-); R^2 is selected from O or S; R^3 is selected from O, S, -SO, -SO_2, -NR^8, C=O, or -C_{1-6} straight or branched-chain alkyl; R^4 is selected from H, C_{1-4} straight or branched-chain alkyl, halogen, -OR^{11} (wherein R^{11} isC_{1-4} straight or branched-chain alkyl optionally substituted by halogen, aryl, C_{3-6} cycloalkyl, (C_{1-3} alkyl-C_{3-6} cycloalkyl), C_{2-6} alkynyl), methylenedioxy, -CX_3(wherein X is halogen,), NO_2, or CN: R^5 is selected from H, halogen or -OR^{11}; R^6 is selected from H, or Y-Ar-$R^7{}_{(m)}$(wherein Y is selected from O, S, -SO, -SO_2, -NR^8, C=O, or -C_{1-6} straight or branched-chain alkyl, Ar is phenyl or naphthyl, m is 1-3 and R^7 is selected from R^8, -CO_2R^8, -COR^8, -$CONR^8R^9$, $R^{8a}OR^8$(wherein R^{8a} is selected from C_{1-6} straight or branched-chain alkyl, and aralkyl), -CN, -CX_3(wherein X is halogen,), -OR^8, OCX_3(wherein X is halogen,), -SR^8, -SO_2R^8, -$OR^{8a}O$-(when m=1), -NO_2, -NR^8R^9, -$NHCOR^8$, -$NHSO_2R^8$, fluoro, chloro, bromo or iodo, or a combination thereof): provided that when R^1 is H, $CH_2OCH_2CH_2OH$ or $CH_2OCH(CH_2OH)_2$, R^2 is O, R^3 is -CH_2 then R^4, R^5 and R^6 are other than -OCH_3, -OCH_2CH_3, -OCH_2Ph, or -O-iso-propyl.

2) A compound of formula (IA)

(IA) 

and esters and prodrugs thereof wherein R^{10b} is C_{2-3} straight or branched chain alkyl group substituted by one or two hydroxyl groups; R^{4a} is H or $-OR^{11a}$ wherein R^{11a} is a C_{3-5} straight or branched chain alkyl group optionally substituted by fluoro; and R^{6a} is H or -O-Ar-R^{7a} wherein Ar is phenyl and R^{7a} is fluoro, chloro or cyano; provided that one but not both of R^{4a} and R^{6a} is H.

3) A compound of formula (IA) according to Claim 2 and esters and prodrugs thereof wherein R^{10b} is $-CH_2CH_2OH$ or $CH(CH_2OH)_2$, R^{4a} is $-OCH_2CH_2CH_3$ or $-OCH(CH_3)CH_2CH_3$ and R^{6a} is H.

4) A compound of formula (IA) according to Claim 2 and esters and prodrugs thereof wherein R^{10b} is CH_2CH_2OH or $CH(CH_2OH)_2$, R^{4a} is H and R^{6a} is-O-Ar-R^{7a} wherein Ar is phenyl and R^{7a} is H, fluoro, chloro or cyano.

5) A compound of formula (IA) according to Claim 2 and esters and prodrugs thereof wherein R^{10b} is CH_2CH_2OH or $CH(CH_2OH)_2$, R^{4a} is H and R^{6a} is -O-Ar-R^{7a} wherein Ar is phenyl and R^{7a} is 3-fluoro, 3-chloro or 3-cyano.

6) A compound of formula (I) for use in medicine.

7) A compound of formula (I) for use as a uridine phosphorylase inhibitor.

8) A compound of formula (I) for use in reducing the cellular toxicity associated with the administration of a pyrimidine nucleoside.

9) A compound of formula (I) for use in reducing the toxicity of neoplastic pyrimidine nucleosides and/or potentiating the efficacy of anti-neoplastic drugs.

10) A compound of formula (I) for use in the treatment of nervous disorders and conditions in which increased levels or uridine are beneficial.

11) Use of a compound of formula (I) in the manufacture of a medicament for reducing the cellular toxicity associated with the administration of a pyrimidine nucleoside.

12) Use of a compound of formula (I) in the manufacture of a medicament for reducing the toxicity and /or potentiating the efficacy of antineoplastic drugs.

13) Use of a compound of formula (I) in the manufacture of a medicament for the treatment and /or prophylaxis of nervous disorders and conditions in which increased levels of uridine are beneficial.

14) A method of reducing the cellular toxicity associated with the administration of a pyrimidine nucleoside which comprises the administration of a pharmaceutically effective amount of a compound of formula (I)

15) A method of reducing the toxicity and/or potentiating the efficacy of an antineoplastic drug which comprises the administration of a therapeutically effective amount of a compound of formula (I)

16) A method of treatment and/or prophylaxis of nervous disorders and conditions in which increased levels of uridine are beneficial which comprises the administration of a therapeutically effective amount of a compound of formula (I).

17) A method of treatment and/or prophylaxis of AIDS-type diseases which comprises the simultaneous or sequential administration of a pyrimidine nucleoside and a compound of formula (I).

18) A method of treatment and/or prophylaxis of an HIV infection in a mammal which comprises the administration of an effective amount of zidovudine or a pharmaceutically acceptable ester or salt thereof in combination with an effective amount of a compound of formula (I).

19) A method of treatment and/or prophylaxis of tumours in a mammal which comprises the administration of an effective amount of 5-fluorouracil in combination with an effective amount of compound of formula (I).

20) A compound of formula (I) in combination with a pyrimidine nucleoside or anti-neoplastic agent.

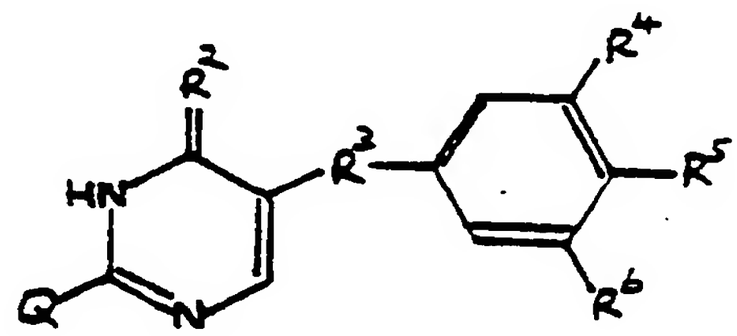
21) A compound of formula (I) in combination with a pyrimidine nucleoside according to Claim 18 wherein the pyrimidine nucleoside is zidovudine.

22) A compound of formula (I) in combination with an anti-neoplastic agent according to Claim 18 wherein the anti-neoplastic agent is 5-fluorouracil.

23) A pharmaceutical formulation comprising a compound of formula (I) and optionally containing a pyrimidine nucleoside or antineoplastic agent together with at least one pharmaceutically acceptable carrier or excipient therefor.

24) A process for the preparation of a compound of formula (I) which comprises

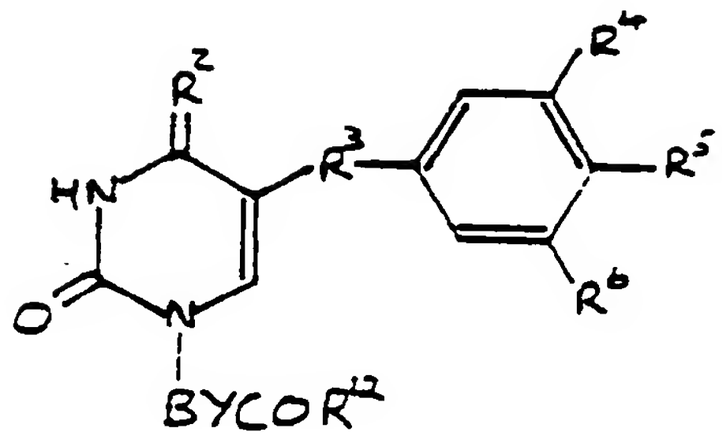
a) the hydrolysis of a compound of formula (II)

(II) 

wherein R^2 to R^6 are as hereinbefore defined and Q is NH_2, OR^{13} or SR^{13} wherein R^{13} is C_{1-6} straight or branched chain alkyl, and thereafter the optionally attaching a group R^1 wherein R^1 is as hereinbefore defined other than hydrogen;

b) where R^1 contains at least one -OH or $-NH_2$ moiety, the hydrolysis of a compound of formula (III)

(III)



wherein R^2 to R^6 are as hereinbefore defined, B is that portion of R^1 other than -OH or $-NH_2$, Y is O or NH and R^{13} is a C_{1-6} straight or branched-chain alkyl group, C_6H_5 or substituted anyl; or

c) by hydrolysis of the O-timethylsilyl ether.

INTERNATIONAL SEARCH REPORT

PCT/GB 93/01443

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D239/54; A61K31/505; C07D239/56

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	WO,A,8 909 603 (BROWN UNIVERSITY RESEARCH FOUNDATION) 19 October 1989 Page 3, first paragraph, Page 5, table I	1-24
X	US,A,4 613 604 (SHIH) 23 September 1986 see column 2, line 5 - line 18	1-24
X	J.HET.CHEM. vol. 29, no. 4, 1 July 1992, pages 683 - 689 BAI-CHUAN 'Synthesis of some Halogenated and Disubstituted Amino Benzylacylcouridine Derivatives'	1-24

-/--

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
17 SEPTEMBER 1993	29. 09. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	GETTINS M.P.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	US,A,5 077 280 (SOMMADOSSI) 31 December 1991 Table I in columns 3 and 4 see column 2, line 9 - line 18	1-24
Y	WO,A,9 116 315 (BROWN UNIVERSITY RESEARCH FOUNDATION) 31 October 1991 see page 1, line 5 - line 10; claim 1	1-24
Y	EP,A,0 449 726 (MITSUBISHI KASEI CORPORATION) 2 October 1991 see claim 1	1-24
A	JP,A,63 290 867 (SDS BIOTECH) 28 November 1988	1-9

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9301443
SA 76255

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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US-A-4613604	23-09-86	None		
US-A-5077280	31-12-91	WO-A-	8909603	19-10-89
WO-A-9116315	31-10-91	US-A-	5141943	25-08-92
		AU-A-	7776891	11-11-91
		EP-A-	0526537	10-02-93
EP-A-0449726	02-10-91	JP-A-	3284670	16-12-91
		JP-A-	3284624	16-12-91
JP-A-63290867	28-11-88	None		

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82